Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JANUARY—1960
Volume 10 - Number 1

Today she is a babysitter—with her own grandchildren. Yet even a generation before she might never have known the joys of marriage and family. Here is a story shared by thousands who lead active lives today because of modern anticonvulsant therapy. Rarely has the progress of medicine touched so many lives with such drama and humanity. Presented here are five distinguished anticonvulsants. They can help you give the most precious of all gifts: a normal life.

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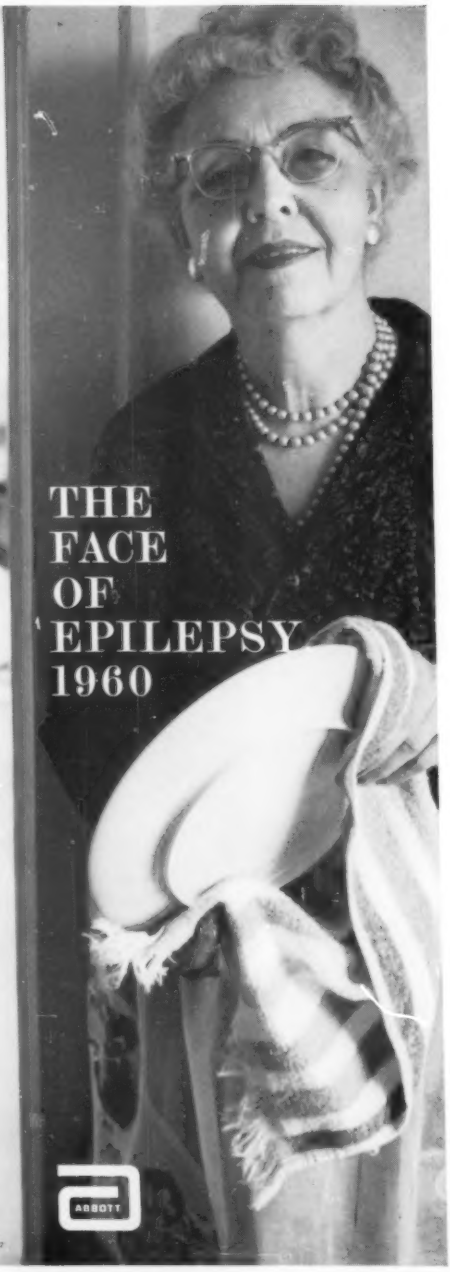

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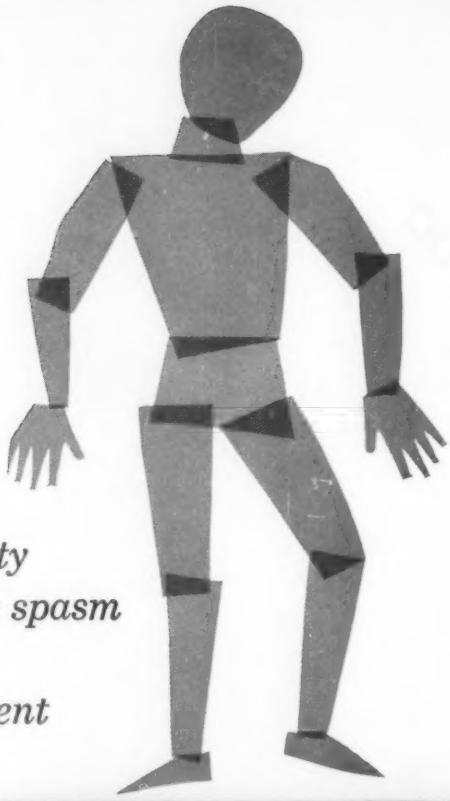
1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.



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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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References: 1. Frain, M.K.: J. Nerv. & Ment. Dis. *125*:529 (Oct.-Dec.) 1957. 2. Graffeo, A.J.: New York State J. Med. *58*:2056 (June 15) 1959. 3. Lesse, S.: Am. J. Psychiat. *113*:984 (May) 1957.

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*Green, J. R., & Steelman, H. F: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1956, p. 136.

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2. Doshay, L. J.: Parkinsonism and Its Treatment, Philadelphia, J. B. Lippincott, 1954, pp. 87-88.
3. Doshay, L. J., Constable, K., and Zier, A.: Neurology *3*:360, 1953.

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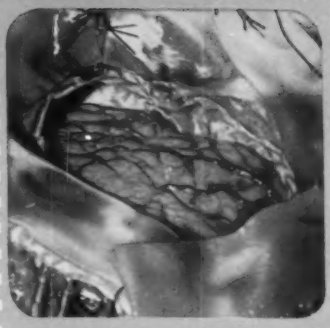

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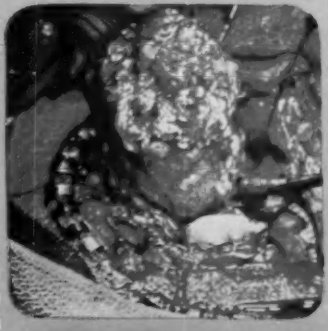

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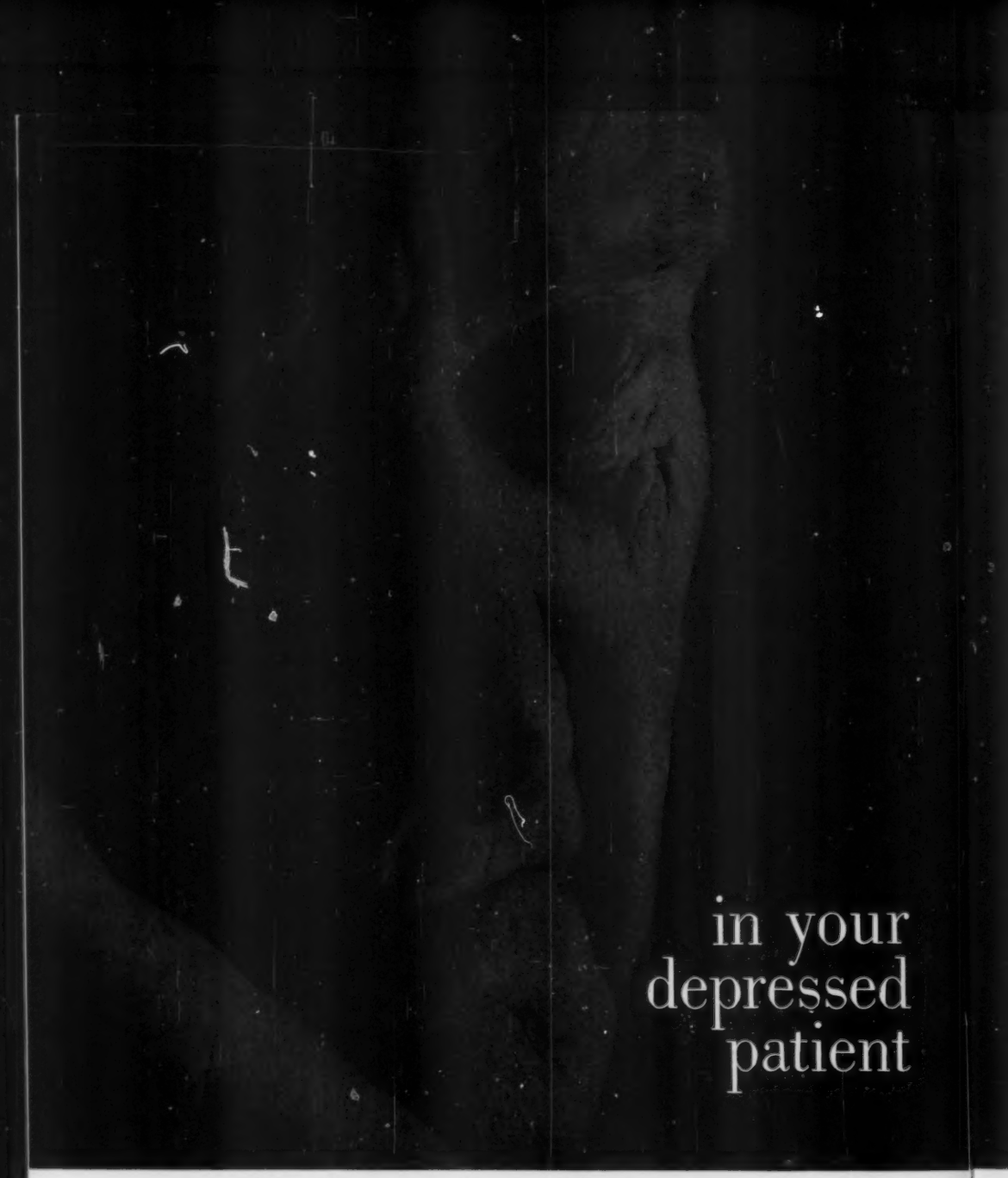

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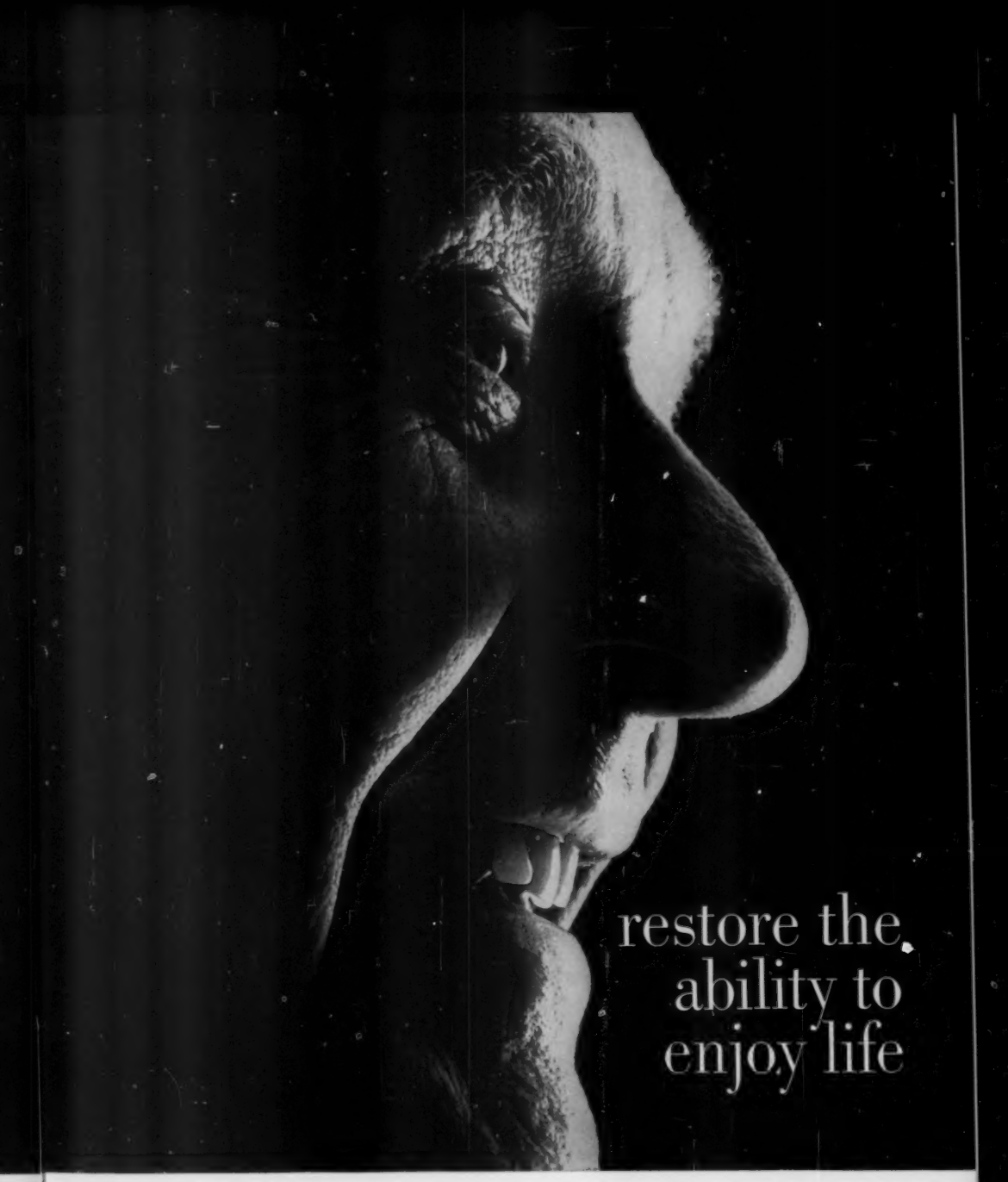

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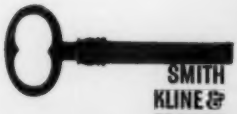
1. Allen, V. S.: Trifluoperazine in the Treatment of Drug-Resistant Schizophrenics, J. Clin. & Exper. Psychopath. *20*:247 (Sept.) 1959.



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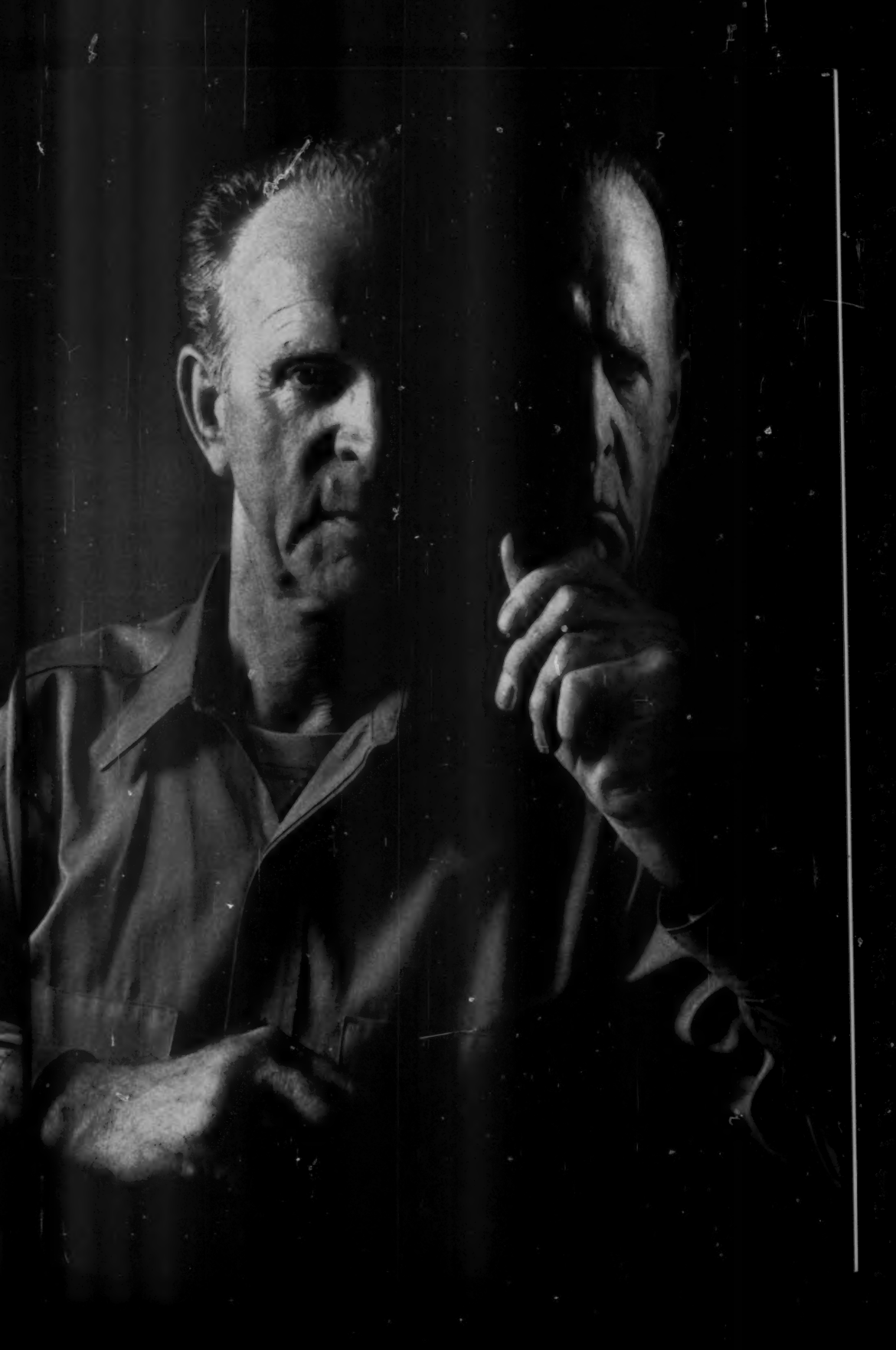

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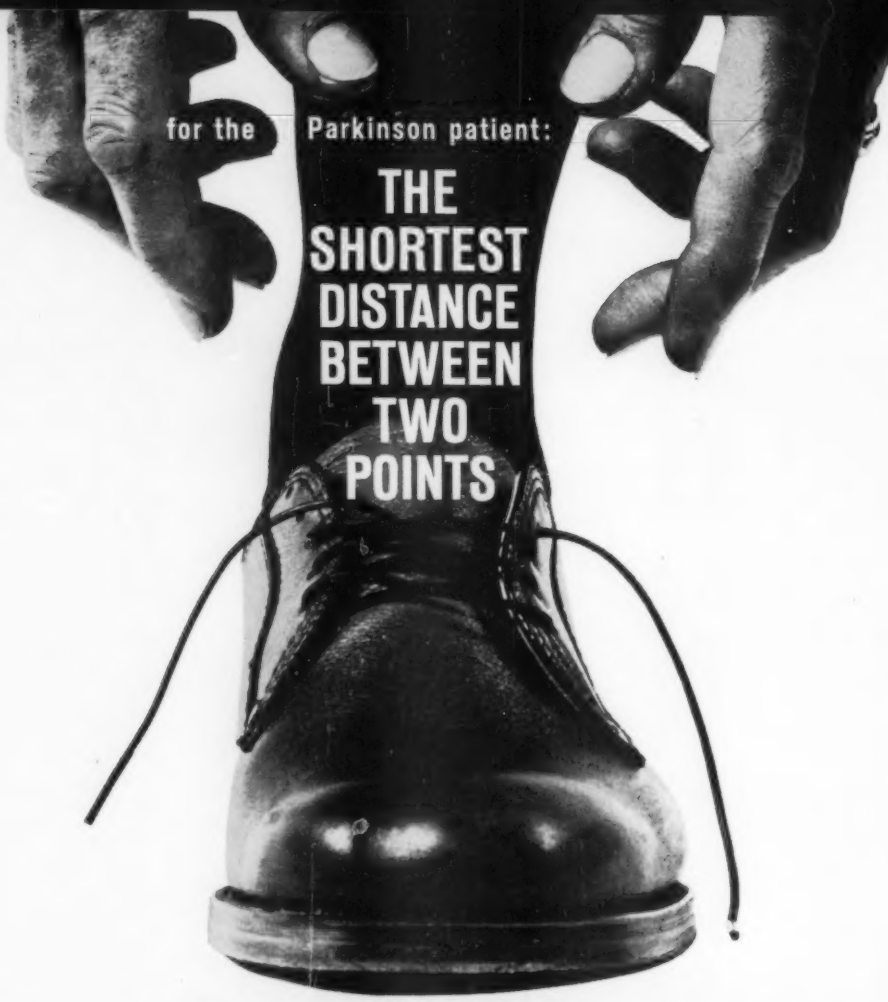

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1. Doshay, L. J.: M. Clin. North America 40:1401 (Sept.) 1956.
2. Doshay, L. J.: Current M. Dig. 22:11:49 (Nov.) 1955.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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Neurology Volume 10 • Number 1

Prolonged behavioral disturbances as ictal phenomena

Eli S. Goldensohn, M.D., and Arnold P. Gold, M.D.*

THE RELATIONSHIP between abnormal behavior and cerebral physiology has long interested the neurologist. Following the introduction of electroencephalography, a number of attempts were made to correlate problems of behavior in children with electroencephalographic abnormalities.[1–5] Despite the absence of evidence of organic brain damage, many of the children were reported to have abnormal electrical activity. In one such study,[4] 74% of children in the 4- to 9-year-old age group with behavior disorders were found to have abnormal records as compared to a control group in which 43% showed abnormalities. A recent study[6] of electroencephalograms in children who were specially selected because of absence of neurologic or psychiatric disturbances both in themselves and in their families showed 42% to be abnormal by the criteria of Gibbs, Gibbs, and Lennox.[7] This high incidence of "abnormality" in normal children brings the significance of the findings in children with behavior disorders into question. Investigations[8–11] of patients of all ages with a wide variety of chronic behavioral and psychiatric disorders report changes in organization, frequency, and paroxysmal patterns. No consistent relationship has been found, however, between electroencephalographic abnormalities and chronic behavioral and psychiatric disorders.[12]

Putnam and Merritt[13] described electroencephalographic abnormalities in "subliminal" epileptic states which interfered with intellectual functions and were characterized by dullness, mental retardation, apathy, and confusion. They stressed that the objective means of differentiation between these seizure phenomena and other behavioral disturbances, such as psychologic reactions and the sedative action of drugs, could be made by the electroencephalogram. They cited a high degree of correlation in time between the prolonged alterations of intellectual function and the abnormal electrical activity.

The most common ictal phenomena associated with behavioral disturbances are psychomotor seizures. Most of these are related to abnormalities in the temporal lobe. Gibbs, Gibbs, and Fuster[14] demonstrated that, be-

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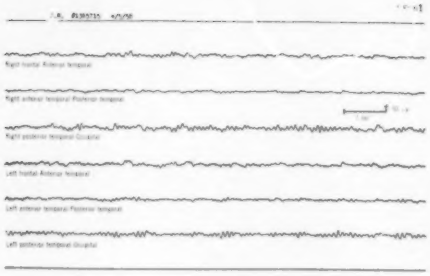

Fig. 1a. Before a prolonged attack. Well organized record with dominant activity at 10 cps.

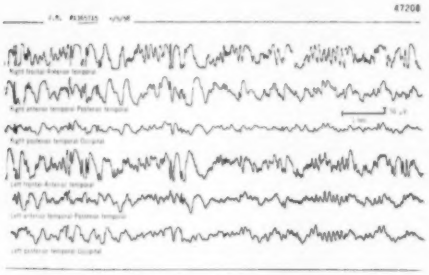

Fig. 1b. During attack. High voltage 9- to 10-cps paroxysm, with a bifrontal accentuation interrupted by 3- to 5-cps spike and wave discharges.

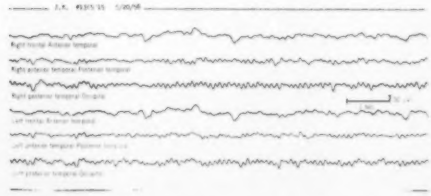

Fig. 1c. Six weeks later. Moderately disorganized and slow without paroxysmal activity

tween psychomotor attacks, spike foci localized to one or both anterior temporal regions were frequently encountered. During psychomotor seizures, the electrical abnormalities follow no specific pattern. Recently, Fuster, Castells, and Rodriguez Barrios,[15] Glaser and Golub,[16] and Glaser and Dixon[17] described patients with psychomotor seizures whose ictal and interictal electroencephalograms showed generalized spike and wave discharges. They emphasized that psychomotor seizures associated with such bilaterally synchronous electrical discharges could not be differentiated clinically from those associated with the more usually encountered temporal lobe spike foci.

The present report describes a series of patients whose seizures present as prolonged behavioral, emotional, and intellectual disturbances appearing simultaneously with generalized abnormalities in the electroencephalogram.

CASE REPORTS

Case 1. J.R., an 11-year-old, normally developed girl, was usually alert, bright, and cooperative. She was the product of a normal pregnancy and delivery, and the neonatal period was unremarkable. She achieved normal milestones until 8 years of age, when she first presented with episodes that her mother described as "sleepy spells" and the referring physician called "a form of narcolepsy." The episodes, which occurred twice weekly, began approximately one hour after being awakened in the morning and lasted up to four hours each. There was no warning of an impending attack, and there were no sequelae. During an attack, the child appeared to be dazed and showed drooping of the eyelids. Although at such times there was slowing in both intellectual and motor spheres, she was able to continue to some extent with her school work or play in a slow, confused, and obtunded manner. She replied hesitantly to all questions but was oriented for person, time, and place. At no time did complete loss of consciousness occur, and memory was preserved for all events that occurred during the episodes. She did not herself recognize her psychomotor retardation but did describe her surroundings as having been "out of focus" or "distant." During the episodes, she sometimes demonstrated brief, intermittent, sudden symmetric jerking of both arms.

She never experienced other ictal disturbances of any kind. Routine laboratory studies, including skull x-rays, fasting blood sugar, cerebrospinal fluid analysis, and serum calcium, were within normal limits.

An electroencephalogram was obtained during a period of obtundation that lasted twenty-seven minutes. Before the episode, the record (Fig. 1a) was well organized with 10-cps activity dominant in the posterior areas and moderate amounts of low voltage fast activity present anteriorly. Small amounts of mainly low voltage, 4- to 7-cps waves were present generally. During the attack, medium and high voltage, paroxysmal, 9- to 10-cps activity appeared in all regions with a bifrontal accentuation. This activity was frequently interrupted by bilaterally synchronous discharges in all leads of

3- to 5-cps spike and wave complexes and multiple and single spikes at highest voltage bifrontally (Fig. 1b). The spike and wave discharges were sometimes accompanied by myoclonic jerks.

Dilantin, 200 mg., and phenobarbital, 30 mg., daily have effected complete control of the attacks.

An electroencephalogram taken six weeks after the initial tracing (Fig. 1c) was moderately disorganized and slow. There was no paroxysmal activity either in the basic record or in response to photic stimulation. Hyperventilation resulted in high voltage, synchronous, 1- to 3-cps waves with a bioccipital accentuation.

Case 2. E.S., a 40-year-old, white, successful salesman, was apparently well until 14 years of age, when he first experienced episodes characterized by confusion and accompanied by rage, screaming, and aggressive behavior. These episodes persisted, and, at 36 years of age, he presented with even more prolonged and pronounced changes in his behavior and state of awareness of twelve to eighteen hours in duration, which he described as "blackout spells" or "foggy attacks." These were not preceded by any aura and could be recalled only with great difficulty. Physicians who observed him described the prolonged periods of abnormal behavior as "fugues." During the attacks, he appeared confused and slowed in both intellectual and motor spheres but was able to continue with simple work. During one attack, he was seen to get out of the hospital bed without any clothes and to walk about aimlessly from room to room. He gave monosyllabic answers to some questions and did not respond to others. The episodes cleared spontaneously without postictal symptoms.

There was a question of a recent major seizure, which could not be confirmed. The family history was negative for convulsive disorders. The general physical and neurologic examinations were normal, and routine laboratory studies, including skull x-rays and cerebrospinal fluid analysis, were negative. The admitting diagnosis was "Functional Disorder."

An electroencephalogram (Fig. 2a) obtained during a "foggy" episode revealed almost continuous high voltage, multiple rapid spikes and multiple spike and wave discharges at various frequencies but most often recurring at about twice per second. On a few occasions of about thirty seconds each, the spikes and spike and wave activity disappeared and were replaced by low to medium voltage, irregular, 6- to 9-cps waves and low voltage rapid activity.

A second electroencephalogram (Fig. 2b) taken two weeks later during an asymptomatic period was strikingly different and contained no evidence of the previously noted paroxysmal activity. The record was considered mildly disorganized and slow.

The patient has had no further attacks since treatment with Dilantin, 300 mg., and Mebaral, 400 mg., daily.

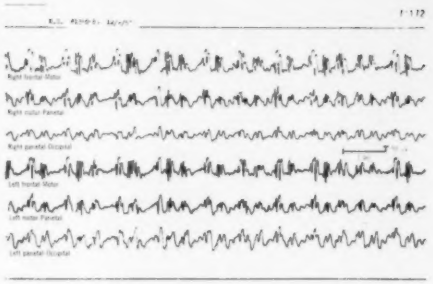

Fig. 2a. During attack. High voltage, multiple rapid spikes and multiple spike and wave discharges recurring at about twice per second

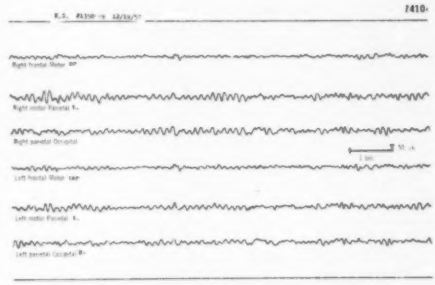

Fig. 2b. Two weeks later. Mildly disorganized and slow. No paroxysmal activity

Case 3. B.B., a 10-year-old white female, did well until 27 months of age, when she was first noted to have staring spells of a few seconds' duration. These continued in an intermittent manner until the age of 7 years, when 5 generalized major seizures occurred during a six-month period. Later, weekly episodes of falling with unresponsiveness lasting ten to fifteen minutes occurred.

At 9 years of age, she was referred for evaluation of episodic behavioral changes. These were described by her mother, a registered nurse, as "dreamy," "lethargic," or "catatonic" periods associated with hostile, negativistic, and uncooperative behavior. During such periods, the child was conscious but frequently refused to follow commands and could continue with her school work or play only in a very slow, hesitant manner. Questions were answered, but the responses were frequently either abusive or inappropriate. Speech became slurred, and facial expressions and grimaces appeared to be employed instead of words. At such times, the child was particularly hostile toward her mother, who felt her to be stubborn and psychotic and probably in need of institutionalization. The episodes occurred at least 3 to 4 times weekly

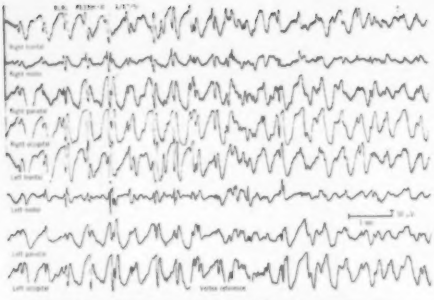

Fig. 3a. During attack. Almost continuous, high voltage 2-cps spike and wave activity

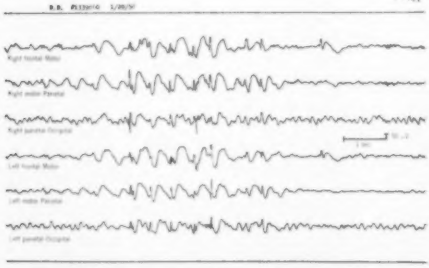

Fig. 3b. Three days later. Bursts of 2- to 2½-cps spike and wave complexes in all leads

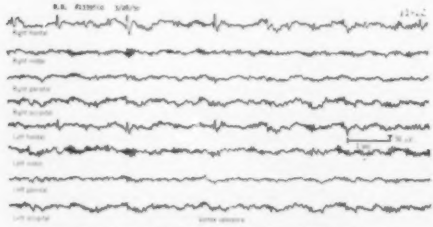

Fig. 3c. Ten weeks later. Bifrontal high voltage spikes with right accentuation. Rapid background activity possibly related to barbiturates

and were approximately twelve to twenty-four hours long. The child stated that they were preceded by "feeling funny." Following the onset of the periodic behavioral abnormalities, there had been a progressive deterioration in her intellectual capacities.

There was no family history of convulsive disorders, and the physical examination was essentially normal. Laboratory studies including skull x-rays and cerebrospinal fluid analysis were within normal limits.

An electroencephalogram was obtained during what was described by the mother as a "catatonic state." Immediately before the electroencephalogram, it was thought by the examining physician that these changes in behavior could be attributed to sleepiness, stubbornness, or lethargy from oversedation. The electroencephalogram revealed almost continuous high voltage, 2-cps spike and wave activity for thirty minutes (Fig. 3a). Then, the spike and wave discharges became intermittent, and, as the bursts shortened in duration, the patient became more alert and pleasant. After a responsive period of ten minutes, there was a return to almost continuous high voltage spike and wave activity with concomitant return of behavioral changes. Three days later, the electroencephalogram (Fig. 3b) was markedly improved but showed many bursts of 2- to 2½-cps spike and wave complexes lasting up to twenty-five seconds each and accompanied clinically by unresponsiveness and fluttering of the eyelids.

Before the institution of medication, psychometric examination classified the patient as defective with a verbal performance of 65 and an over-all I.Q. of 59. Receiving Tridione, 1,800 mg., Mysoline, 250 mg., Celontin, 900 mg., and phenobarbital, 100 mg., daily, the child no longer presented with episodes of prolonged behavioral changes and became cheerful, outgoing, and friendly. Her school work has shown marked improvement, and a recent psychometric examination classifies the child as borderline normal with a verbal performance of 89 and an over-all I.Q. of 76. Recently, she again has had short seizures, which consist of falling backward followed by picking up and moving objects, running about the house, mumbling, swallowing, and chewing. An electroencephalogram (Fig. 3c) taken after the return of the above attacks showed bifrontal high voltage spike activity with a right accentuation and rare 2- to 2½-cps generalized spike and wave bursts.

Case 4. R.A., a 16-year-old girl, was delivered as an uncomplicated breech from a full term twin pregnancy and weighed 5 lb., 7 oz. at birth. Milestones were achieved normally until 3½ years of age, when she first had monthly episodes of cyclic vomiting associated with unusual behavior of up to three days in duration.

The attacks began with periumbilical discomfort and vomiting. During the spells, she was withdrawn and had numerous vomiting and retching episodes. She did not respond readily to questions but was aware of her environment. When she reacted, she was antagonistic toward her parents and pushed them aside and screamed. After several days, the spell would stop abruptly and could be recalled with little difficulty. The prolonged vomiting caused such marked changes in electrolyte balance that 24 hospital admissions were required. Over a period of years, the child had become progressively more unhappy and there had been an increase in impulsivity, egocentricity, dependency, and frustration.

At 4 years of age, brief staring episodes were first noted, which were diagnosed as petit mal. Leukopenia developed while she was receiving Tridione, and a combination of Mesantoin, Dilantin, and phenobarbital was unsuccessfully employed in the management of her small attacks.

The family history is pertinent in that the patient's identical twin sister had a similar clinical picture with the triad of abdominal pain, vomiting, and unusual behavior. She too required many hospitalizations and, at 15 years of age, died of a perforated esophageal ulcer.

General physical examination was unremarkable except for obesity and a peculiarly rounded facies. The neurologic examination and laboratory studies, including skull x-rays, pneumoencephalogram, cerebrospinal fluid analysis, serum calcium and phosphorus, blood sugars, and nonprotein nitrogen, were within normal limits.

In the midst of a typical three-day attack of abdominal pain, vomiting, and behavioral changes, an electroencephalogram (Fig. 4a) revealed a continuously paroxysmal record characterized by high voltage, 2½- to 3-cps spike and wave discharges. The technician noted that the paroxysmal activity increased in amount and amplitude when the child complained of increasing abdominal discomfort or began to vomit.

The readministration of Tridione resulted in a decrease in frequency, severity, and duration of the prolonged attacks. The petit mal attacks also markedly diminished. There was a considerable improvement in personality and behavior, and the patient became interested in others, took pride in her appearance, and became less dependent and demanding. An electroencephalographic tracing (Fig. 4b) two months after the reinstitution of Tridione was markedly improved but abnormal with many 4- to 6-cps waves and rare 4-cps spike and wave discharges. A subsequent tracing taken four months later was only mildly and nonspecifically abnormal. She now receives Dilantin, 200 mg., phenobarbital, 45 mg., and Tridione, 1,800 mg., daily.

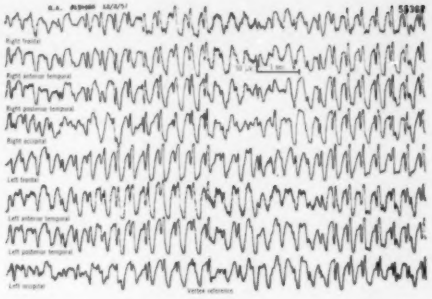

Fig. 4a. During attack. Continuous, high voltage 2½- to 3-cps spike and wave discharges

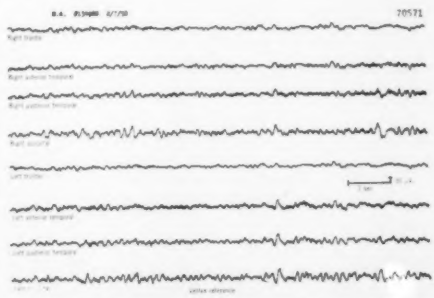

Fig. 4b. Two months later. Moderately abnormal with many 4- to 6-cps waves

Case 5. H.K., a 25-year-old chemical engineer, was born at term following a normal uncomplicated delivery. Infancy was unremarkable except for one generalized convulsion associated with fever.

At 5 years of age, episodes began which were characterized by sudden transient arrest of all activities and by eyelid blinking and facial grimacing. These attacks have persisted and recently have sometimes been associated with lip smacking and a peculiar posturing of the fingers. At 15 years of age, he experienced a generalized major seizure with loss of consciousness. Despite therapy with Dilantin, phenobarbital, and Mysoline, the seizures recurred approximately monthly. The patient nevertheless successfully completed high school and college, earning a degree in chemical engineering.

At 23 years of age, episodic prolonged impairment of mental processes with slowing of speech and motor activity was noted. During the episodes, his attention was attracted to trivia, such as a loose thread in a rug which he would examine minutely. He appeared timid and quiet but was nevertheless obstreperous if crossed. Although confused and withdrawn, he followed commands in a slow, often incomplete and irrelevant manner. The patient himself described these episodes as "dreamy spells" and stated that "it is as if one is looking at the world through a fog." These prolonged periods of behavioral changes were easily recognized by the patient, his family, and his employer. They were not preceded by any warning and occurred at least once or twice weekly, with durations of between four and twelve hours. Because of impaired efficiency that resulted from the attacks, he was given less intellectually demanding work. He was, however, unable to adequately perform even clerical duties, and his position with an engineering firm was terminated.

There was no family history for convulsive disorders. The physical examination was unremarkable. Laboratory studies, including x-rays of the skull, pneumoencephalogram, cerebrospinal fluid analysis, serum calcium and phosphorus, blood urea nitrogen, and blood sugar determinations, were normal.

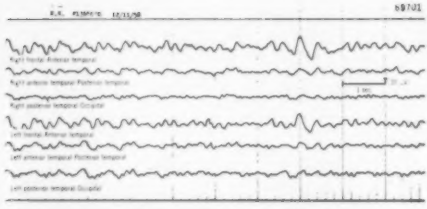

Fig. 5a. During attack. Grossly disorganized and slow with continuous slow activity between 2 and 5 cps.

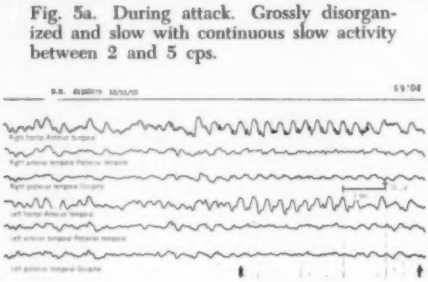

Fig. 5b. During attack. Bursts of 3-cps spike and wave complexes appear from time to time. Patient failed to continue counting during time between arrows.

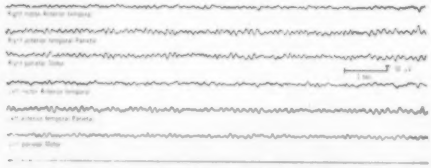

Fig. 5c. Symptom-free period. Well organized with 9-cps waves posteriorly and low voltage fast activity anteriorly

Although psychometric examination during an asymptomatic period revealed an I.Q. of 115, during his prolonged "dreamy states" he had difficulty in comprehension and in solving simple mathematical problems.

The electroencephalogram during a period of prolonged behavioral change (Fig. 5a and b) was grossly disorganized and slow with continuous 2 to 5-cps waves at medium and high voltage in general distribution and 3-cps spike and wave complexes appearing from time to time bilaterally with a marked bifrontal accentuation. The bursts of 3-cps spike and wave activity were sometimes associated with a depression of consciousness and a failure to continue counting. The tracings (Fig. 5c) taken when the patient was not in the "dreamy state" were characterized by fairly frequent, short 3-cps spike and wave bursts against a background of well organized, 8- to 9-cps activity in the posterior areas and moderate amounts of low voltage fast activity anteriorly.

Attempts at controlling the petit mal and generalized major seizures and the "dreamy" periods have been only partially successful with Dilantin, 400 mg., Tridione, 2,400 mg., and phenobarbital, 60 mg., daily.

DISCUSSION

Both the children and adults in our series have in common prolonged behavioral changes and associated electrical recordings of generalized bilaterally synchronous paroxysmal activity. The prolonged behavioral changes were characterized by a rapid onset and termination of confusion, hostility, negativism, withdrawal, and fogginess or dreamy state usually associated with motor activity ranging from myoclonic jerks, lip smacking, and finger posturing to complicated, apparently purposeful activity. There was never complete loss of consciousness, but there was some degree of loss of awareness and a moderate to marked depression of intellectual functions. All except possibly 1 patient could accurately recall the events that occurred during the attacks. Because of the maintenance of consciousness and duration of the symptoms, some of the patients were at first considered to be psychoneurotic or psychotic.

It was Jackson's[18] belief that most and perhaps all automatic "mental" behavioral states associated with epilepsy were actually postepileptic and resulted from paralysis of the higher centers. He suggested that the changes in mental state which lasted for hours were similar in mechanism to the postictal hemiplegia described by Todd. Later Gibbs, Gibbs, and Lennox[19] with the aid of electroencephalography demonstrated that short automatisms occur during seizures. Putnam and Merritt[13] showed that some prolonged behavioral disturbances can be ictal phenomena, thus demonstrating that changes in mental function during seizures need not be characterized by short duration. These authors also noted the importance of the electroencephalogram for distinguishing seizures from other mental changes of either a functional nature or related to drug intoxication. The electroencephalographic abnormalities they described during periods of intellectual changes included wave and spike patterns and slow wave activity.

Tucker and Forster[20] subsequently described 2 patients as being in petit mal status, who had prolonged states of confusion and unusual behavior. These periods were associated with recurrent prolonged bursts of 3-cps spike and wave activity. The petit mal status was terminated by the inhalation of carbon dioxide in 1 patient, and both were brought under control with trimethadione. The authors remarked on the difficulty in clinical differentiation among petit mal status, psychomotor seizures, and psychogenic disturbances. Subsequently, other reports[21–25] on prolonged petit mal and petit mal status with mental changes and concomitant 2- to 3-cps spike and wave activity have been made. Many of the patients were described as being in a psychomotor-like state. They usually responded well to therapy with trimethadione or diphenylhydantoin sodium. The report of Kellaway and Chao[25] described children with petit mal status who had sudden deterioration in both intellectual and behavioral spheres for periods of weeks or even months in association with 2- to 3-cps spike and wave activity predominantly in the parietal and occipital regions. The deterioration suggested the possibility of degenerative disease, but, with effective medication or ketogenic diet, both the clinical and electroencephalographic changes reverted toward normal. What the above reports have called "petit mal status" has also been identified by other names. Friedlander and Feinstein[26] referred to these prolonged seizures as "epilepsia minoris continua." Zappoli[27] preferred the more descriptive designation of "epileptic twilight state with spike-wave," while Bornstein, Coddon, and Song[28] selected the descriptive title of "prolonged alteration in behavior associated with a continuous electroencephalographic abnormality." In view of the prominence of automatic behavior, Schwab[29] also questioned the advisability of referring to these prolonged periods of altered consciousness as "petit mal status." He remarked that spike and wave discharges lasting longer than fifteen seconds were almost always accompanied by automatic movements and clouding of consciousness and therefore preferred the term "short automatism."

Fuster, Castells, and Rodriguez Barrios[15] described patients with similar electrical and clinical pictures as having psychomotor epilepsy. They pointed out that the clinical picture was indistinguishable from psychomotor seizures of temporal lobe origin. They felt that the diencephalic structures responsible for both the clinical and electrical aspects of petit mal could also produce phenomena identical to those that more frequently originate from discharges in the temporal lobe. It is interesting that the automatic behavior associated with discharges originating in the temporal lobe frequently occurs after the cortical paroxysmal electrical activity is over[30] and is therefore postictal, while the behavior asssociated with bilateral spike and wave discharges described by Fuster and associates is ictal. They postulated that abnormal activity begins in the diencephalic nuclei and then activates distant structures that are responsible for automatisms. This interpretation is in keeping with Penfield and Jasper,[31] who describe the mechanisms by which subcortical discharges may spread and activate cortical structures by means of diffuse and specific projections. While activation of the specific projections produces specific cortical phenomena such as motor, visual, and auditory, the diffuse system produces more widespread effects that involve general functions such as consciousness and behavior.

Niedermeyer's[32] patient showed initial temporal lobe spiking followed by generalized synchronous 2½- to 3-cps spike and wave complexes that were associated with clouding of consciousness and automatism. Guinena and Taher[33] reported cases of visual and auditory psychosensory seizures, with loss of consciousness associated with generalized 3-cps spike and wave discharges. The presence of visual and auditory phenomena preceding otherwise classic petit mal attacks suggests that the localizing importance of aura preceding the "secondary automatisms" described by Fuster and associates[15] may be of limited practical significance. The latter had postulated in cases with such aura that firing begins in a temporal focus and spreads by corticofugal pathways to the thalamoreticular structures.

Glaser and his colleagues[16,17] emphasized the relatively frequent occurrence of generalized spike and wave discharges in children with psychomotor seizures as compared to spike foci in the temporal lobe of adults. They re-

lated this difference to the immaturity of the child's cerebral cortex, which allows an easy interplay of electrical activity between the temporal-limbic and thalamoreticular systems. From ontogenetic studies in kittens, it appears that, in the young, spike and wave discharges are a preferred, self-sustained epileptic afterdischarge of relatively normal cortical areas.[34] Since, like Fuster and associates, they were unable to determine any clear clinical differentiation between the seizures of patients with spike and wave electrical activity and those with temporal lobe spikes, the authors regarded the former as having "psychomotor epilepsy." Glaser[35] concluded that bilaterally synchronous 3-cps spike and wave discharges are not specific for centrencephalic epilepsy and do not necessarily indicate an origin in subcortical structures of the midline.

In our patients, the altered behavioral states were demonstrated to be epileptic attacks by the simultaneous recording of continuous or almost continuous generalized paroxysmal electrical activity without focal signs. The most usual patterns were spike and wave complexes at 2 or 3 cps, but rhythmic multiple spike discharges were a prominent feature in 1 case and rhythmic, high voltage, 9- to 10-cps waves in another. In only 2 of the 5 patients was typical 3-cps spike and wave activity present during the prolonged seizures. Although, except for duration, the observed behavioral changes were indistinguishable on clinical grounds from temporal lobe epilepsy, none had electrical abnormalities localized to the temporal lobe. Although it is more likely that activity originating in central subcortical structures discharges widely to the cortex and is responsible for the altered behavioral state, the alternative exists that discharges from medial temporal or other cortical areas inaccessible to scalp electrodes project to and activate the subcortical structures.

The type and duration of symptoms in our patients are also similar to those in the epileptic clouded states described by Levin.[36] His patients, who were admitted to a psychiatric hospital because of prolonged abnormal behavior, did not show seizure activity on the electroencephalogram and were postictal.

Our experience with this group of patients has enlarged our concept of seizure phenomena to include constellations of prolonged mental and emotional symptoms, which formerly we were prone to regard as functional even in individuals known to have other manifestations of epilepsy.

SUMMARY

1. A series of 5 patients, 2 adults and 3 children, is described, in whom episodes of behavioral, emotional, and intellectual disturbances occurred, lasting up to seventy-two hours each.

2. The clinical disturbances were accompanied by simultaneous, continuous or almost continuous, bilaterally synchronous paroxysmal activity in the electroencephalogram.

3. Although the behavioral manifestations were more prolonged, they were in many respects similar to those of temporal lobe epilepsy. There were, however, no signs referable to the temporal lobe in the electroencephalogram, either during or between seizures.

4. The cases demonstrate that prolonged abnormal behavior can be the sole manifestation of a seizure and that such an attack may easily be confused with a functional psychiatric disorder.

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A clinical and pathologic study of akinetic mutism

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AKINETIC MUTISM, a disturbance of consciousness so designated by Cairns, Oldfield, Pennybacker, and Whitteridge,[1] is a clinical condition characterized by absolute mutism and complete immobility except for the eyes. The patient so afflicted generally keeps his eyes open and occasionally appears to follow the movement of objects placed before him. He gives no evidence of pleasure or displeasure or any other response when stimulated by auditory or mechanical means, except for opening the eyes if they happen to be closed. This condition has sometimes been designated as coma vigil. It was first described[1] in a patient with an epidermoid cyst and has also been reported in a variety of other circumstances,[1–7] including basilar artery thrombosis.[8–11]

This paper will describe in detail the clinical and pathologic features observed in 7 cases of akinetic mutism associated with basilar artery thrombosis and, in another case, with illuminating gas poisoning.

CASE REPORTS

Case 1. This 54-year-old man was admitted to the hospital on Dec. 26, 1954, with a history of severe headache, speech difficulties, and weakness of the right side of his body for six hours. When admitted, he was unable to stand and was frothing at the mouth. His blood pressure was 140/90 mm. Hg; pulse rate, 84 per minute; respiratory rate, 26 per minute; and temperature, 96.6° F. He was unable to speak but could make occasional movements with his right arm and leg and with his head. Left facial weakness, spasticity of both legs, and flaccidity of the left arm were present. On painful stimulation, he responded only by slight movement limited to his left leg. Generalized hyperreflexia and bilateral Babinski signs were found. A lumbar puncture showed clear cerebrospinal fluid under normal pressure, containing 65 mg. per cent of total protein. His serum nonprotein nitrogen was 45 mg. per cent. Laboratory examinations of blood and urine were otherwise normal. Plain roentgen films of chest and skull were normal. On the following day, the patient was unresponsive except for his eyes, which were observed to be open and moving spontaneously in all directions. When the eyes were closed, they would open in response to loud noises. A few horizontal nystagmoid jerks were noted bilaterally. The pupils were round, regular, and equal and responded well to light. The right palpebral fissure was smaller than the left. The corneal reflexes were absent bilaterally. His temperature rose to 105° F., and his blood pressure started to fall, reaching a level of 122/66 mm. Hg. On Dec. 30, it was noted that the eyes showed marked limitation of movement in all directions. A Babinski sign was present only on the right side. On Dec. 31, his breathing became very poor, his temperature rose to 106° F., and he died.

Autopsy revealed cardiac hypertrophy, mild coronary atherosclerosis, an old healed myocardial infarct, and mild lobular pneumonia. The basilar and vertebral arteries were markedly tortuous; a large, thick atheromatous plaque was found at the middle of the basilar artery, attached to which was a fresh thrombus that completely occluded the lumen. A very small, pale infarct was noted in the anterior limb of the right internal capsule. The base of the pons was infarcted bilaterally, as well as the ventral portion of the tegmentum including both medial and lateral lemnisci and both trapezoid bodies. The midbrain, medulla, and cerebellum were essentially normal (Figs. 1 and 2).

Case 2. This 55-year-old man was admitted to the hospital on Sept. 11, 1953, because of an infection of the right hand following a thrombosis of the right brachial artery and amputation of 2 fingers. There were no other abnormalities. On

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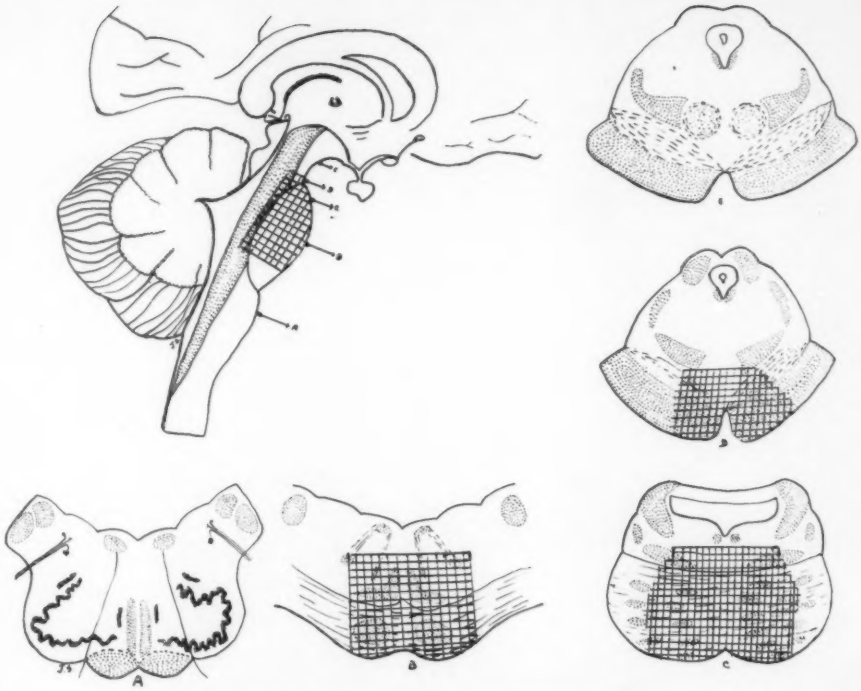

Fig. 1. *Case 1.* Diagram of distribution of lesions in brain stem

Oct. 5, he suddenly began to have transient intermittent episodes of dizziness, dysarthria, drooling, and weakness of the left side of his face. These episodes lasted about fifteen minutes and were followed by complete recovery. There were about 5 such occurrences within a period of about twenty-four hours. Following the last of these incidents, left facial weakness, hemiparesis, and hyperreflexia and bilateral Babinski signs remained. His blood pressure was 160/86 mm. Hg; pulse rate, 140 per minute; respiratory rate, 28 per minute; and temperature, 99.4° F. He appeared restless and apprehensive. He opened and closed his eyes on command but was unable to move his extremities or to talk. Two days later, he was unable to respond in any way to verbal or mechanical stimuli. He appeared motionless and speechless, as if in coma, but his eyes remained open and moved spontaneously in all directions. His temperature was 102.6° F., and his nonprotein nitrogen rose from 31 mg. per cent on admission to 69 mg. per cent. He remained in this condition for the following three days, at which time the deep tendon reflexes were noted to be absent. The left side of his body was cold when compared to the right.

Fig. 2. *Case 1.* Pons, revealing extensive lesion in base and tegmentum. Luxol blue stain. × 5

He began to have difficulties in swallowing. A lumbar puncture revealed a pink cerebrospinal fluid at a pressure of 160 mm. of water, containing 6,480 fresh red blood cells and 9 white blood cells per cubic millimeter. He developed a respiratory

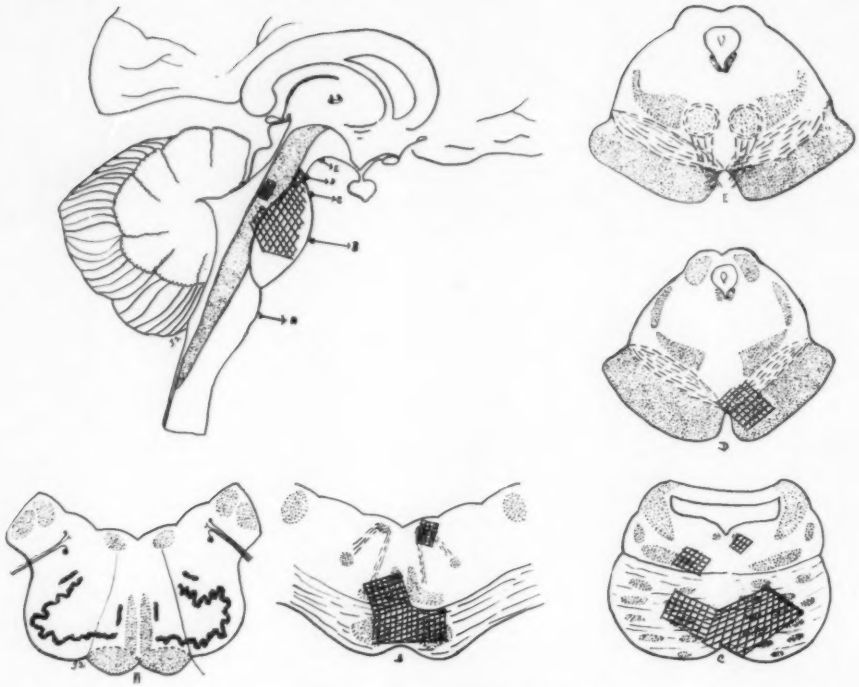

Fig. 3. *Case 2.* Diagram of distribution of lesions in brain stem

infection, and his blood nonprotein nitrogen continued to rise. His general state of consciousness was unchanged until Oct. 21, when he went into shock and, the following day, into deep coma. At this time, his eyes were closed and fixed in the midline. The deep tendon reflexes were absent, and the pupils were dilated. He died on Nov. 1.

Autopsy revealed generalized arteriosclerosis with thrombi in the abdominal aorta, myocardial hypertrophy, lobular pneumonia, bilateral recent pulmonary emboli, acute pyelitis, thrombosis with organization of the right brachial and subclavian arteries and subclavian vein. The brain showed relatively slight atherosclerosis of the vessels of the circle of Willis, except for large atherosclerotic plaques at the bifurcation of the basilar artery and in the proximal portion of the left posterior cerebral artery. A recent thrombus completed the occlusion of the basilar artery at its bifurcation. On section, the cerebrum was normal. The brain stem revealed a fresh infarct of the base of the pons together with small areas of necrosis in the tegmentum, affecting particularly the thalamo-olivary tract and part of the medial lemniscus (Fig. 3). Sections of the medulla, midbrain, and cerebellum showed no lesions.

Case 3. This 70-year-old man was admitted to the hospital on Dec. 21, 1953, with a history of headaches, nausea, vomiting, dizziness, dysphagia, numbness of the right side of the face, and visual difficulties for a few hours. Two weeks before admission, he had had an episode of alexia, lasting for a few minutes. On examination, his blood pressure was 150/110 mm. Hg; pulse rate, 84 per minute; and respiratory rate, 20 per minute. Nystagmus was present on lateral gaze bilaterally, more marked on the left. Corneal reflexes were absent bilaterally. A right peripheral facial paralysis, hypesthesia of the right side of the face and left hand, and slight dysmetria with the right extremities were noted. The routine laboratory examinations, including that of the cerebrospinal fluid, were normal. For two days after admission, there was considerable improvement of all signs and symptoms, except for persistent headache. At this time, he began to complain of ringing in both ears and to experience difficulties in expectoration. His speech became "thick" and then completely unintelligible. The pulse was slow and irregular. A few hours later, there was a transient episode of unconsciousness lasting approximately three minutes, after which he became partially reactive. He

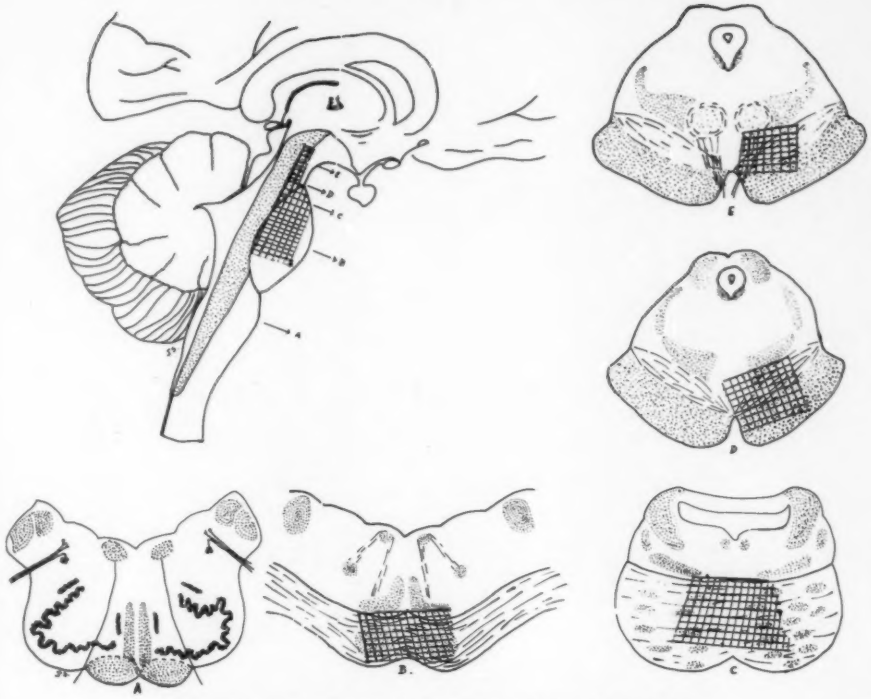

Fig. 4. *Case 3.* Diagram of distribution of lesions in brain stem

would open and close his eyes on command and spontaneously but did not move otherwise. His eyes remained fixed in the midposition, wandering only slightly in the vertical plane. His pupils were miotic but reacted to light. His blood pressure dropped to 105/70 mm. Hg, and he became cyanotic. A few hours later, spontaneous bilateral decerebrate movements of the upper extremities appeared. His pupils became much smaller and no longer reacted to light. All the deep tendon reflexes were active, and a right Babinski sign was elicited. Passive turning of his head in the lateral plane produced a downward and inward deviation of the right eye in a disconjugate fashion, but the left eye did not cross the midline. He remained in this condition for twenty-four hours longer and then died.

Autopsy revealed generalized atherosclerosis, arteriolar nephrosclerosis, tracheobronchitis, and slight cardiac hypertrophy. The arteries at the base of the brain showed marked atherosclerotic changes with considerable narrowing of the lumen, particularly of both vertebral arteries. The proximal portion of the basilar artery was completely occluded by a recent thrombus. Section of the cerebrum revealed a series of cystic areas of degeneration in the white matter of the left occipital lobe and in the most posterior portion of the left parietal lobe. The left visual cortex was also the site of recent infarction. The cerebellum contained cystic infarcts in the central white matter bilaterally. Section of the brain stem revealed infarcts in the basilar portion of the pons on both sides, with minimal involvement of the tegmentum. The infarct extended for a short distance into the midbrain, particularly into the substantia nigra. The medulla was normal (Fig. 4).

Case 4. This 54-year-old man was admitted to the hospital on Nov. 5, 1953, with a history of episodes of spontaneous crying for two weeks. There were several episodes of marked dysarthria accompanied by occipital headache and a sensation of seeing flickering colored lights, each lasting approximately one minute and extending over a period of ten days before admission. At times, these episodes were also accompanied by numbness of the left arm and pain in the right arm. About 4 A.M. on the day of admission, he felt "strange" and, very shortly thereafter, suddenly became anarthric and completely akinetic. On admission, examination revealed his blood pressure

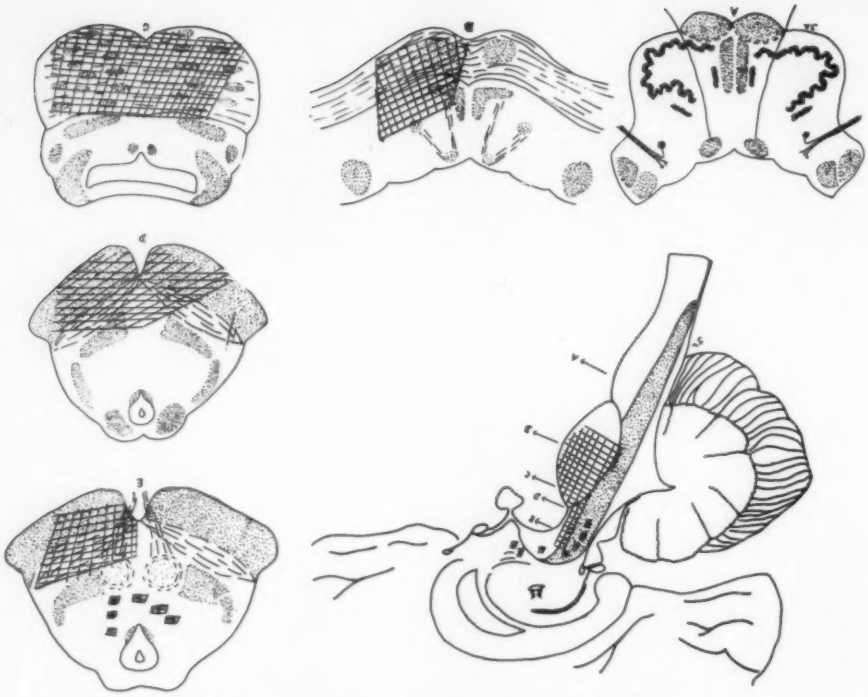

Fig. 5. *Case 4.* Diagram of distribution of lesions in brain stem

to be 180/85 mm. Hg; pulse rate, 74 per minute; respiratory rate, 9 to 15 per minute; and temperature, 104° F. During the first hour of hospitalization, it appeared as if he could move his eyes on command. He seemed to understand what was told to him but could not speak intelligibly, though he mumbled a few totally unrecognizable sounds. Shortly thereafter, he became completely anarthric and incontinent of urine. His pupils were miotic and reacted minimally to light. An inconstant rotary nystagmus bilaterally, left lower facial weakness, and flaccid quadriparesis were present. His arms withdrew slightly on painful stimulation. The deep tendon reflexes were active in the upper extremities, more so on the left, and hypoactive in the lower extremities. There was no Babinski sign. The routine laboratory examinations, including that of the cerebrospinal fluid, were normal. During the next twenty-four hours, he would open his eyes and move them about but would no longer do this on command. There was now a complete akinesia, except for the movement of the eyes. On the third day, his temperature rose to 107° F., his pulse became fast and weak, and he died.

Autopsy revealed bronchopneumonia, moderate cardiac hypertrophy, myocardial fibrosis, and coronary and generalized atherosclerosis. There was generalized atherosclerosis of the arteries of the circle of Willis, with a complete occlusion of the caudal portion of the basilar artery by a recent thrombus. Section of the cerebrum revealed no lesions. Section of the brain stem revealed the basilar portion of the midpons to be soft and friable and to contain petechiae. The most caudal portion of the midbrain appeared similarly affected in part. The medulla and cerebellum showed no lesions. Microscopic study demonstrated the fresh infarct to involve the right peduncle and small areas of the ventral tegmentum of the midbrain. A major portion of the base of the pons was affected bilaterally, although caudally the infarct extended to a greater degree on the right. The medulla appeared intact. Although grossly normal, the visual cortex revealed homogenizing necrosis of neurons microscopically. The hypothalamus contained a few petechiae (Fig. 5).

Case 5. This 58-year-old male was admitted to the hospital on April 23, 1958, because of unconsciousness of two and one-half hours' duration.

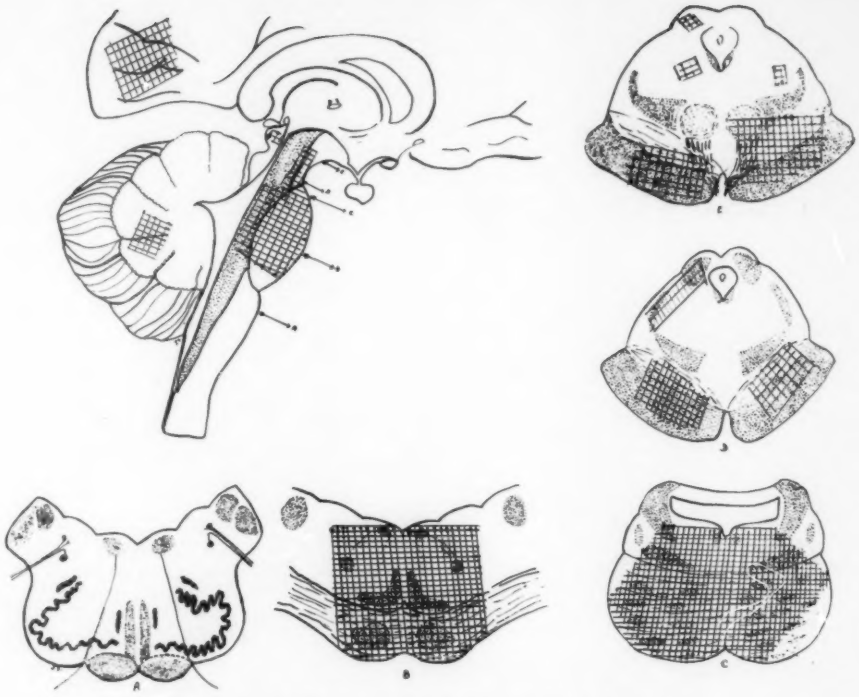

Fig. 6. *Case 5.* Diagram of distribution of lesions in brain stem

He had experienced a number of convulsive seizures of undescribed type, each lasting up to fifteen minutes, over a period of fifteen years before admission. Five years before admission, he had an episode of total blindness of both eyes, sudden in onset, with gradual and almost complete recovery. One month before admission, he had a syncopal attack lasting about one hour, with complete recovery. In the two weeks preceding admission, he complained of severe occipital headache. On examination, his blood pressure was 168/90 mm. Hg; pulse rate, 120 per minute; respiratory rate, 36 per minute; and temperature, 100° F. He was completely out of contact. His eyes were generally open and moved spontaneously at random in all directions. When his eyes were closed, he would open them promptly when stimulated by painful mechanical or auditory means. At times, his head would be turned to one side, while his body was turned to the other. His pupils were constricted but reacted well to light. The corneal reflexes were absent. A very transient decerebrate posture was assumed and could be elicited by painful stimuli. The deep tendon reflexes were symmetrically increased, and there were bilateral Hoffmann and Babinski signs. Routine laboratory examinations, including that of the cerebrospinal fluid, were normal. Chest and skull films, a ventriculogram, and electroencephalogram were normal. On the third day, his temperature rose to 103° F. and his pupils became markedly miotic and no longer reacted to light. The spasticity in all 4 extremities was increased. His eyes stayed open for long periods, moving in all directions, but at times were closed. He developed bronchopneumonia and died May 2, 1955.

Autopsy revealed marked cerebral atherosclerosis with complete occlusion of the basilar and right vertebral arteries by a recent thrombus. An old organized thrombus was found in the right posterior inferior cerebellar artery. A recent anemic infarct was present in the right subthalmus, including 1 corpus luysi and the red nucleus. In the midbrain, minor portions of the lateral reticular substance, a small portion of 1 colliculus, and part of both peduncles were infarcted. A major portion of the base and tegmentum of the pons was destroyed. The medulla was normal. A large, old cystic infarct in the right cerebellum and others in the temporooccipital lobes were found bilaterally, affecting the visual cortex (Fig. 6).

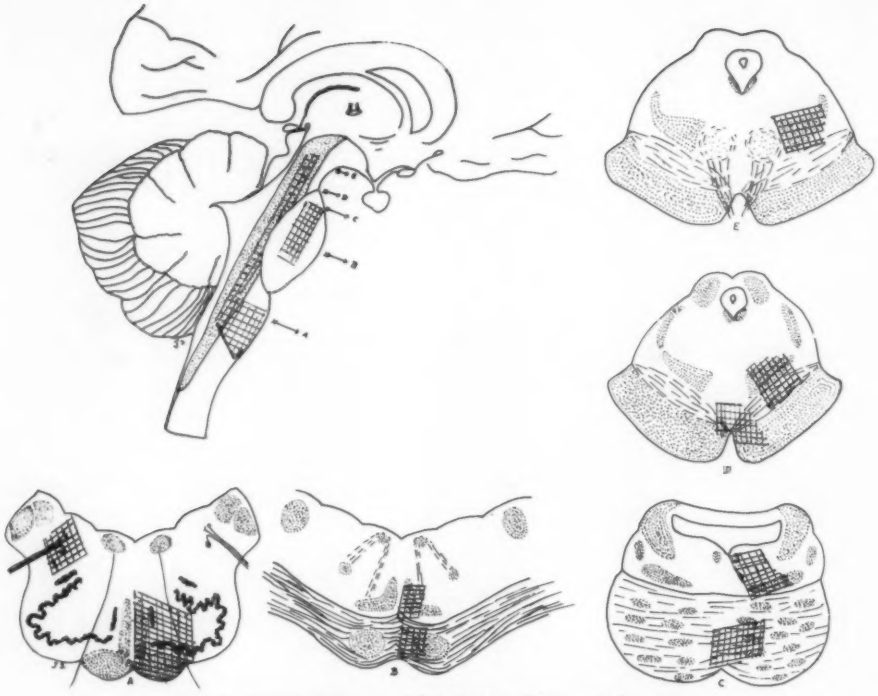

Fig. 7. *Case 6.* Diagram of distribution of lesions in brain stem

Case 6. This 60-year-old man was admitted to the hospital on Jan. 26, 1958, because of progressive weakness of the left leg of one week's duration. On the day of admission, he suddenly fell out of bed and was brought to the hospital. On admission, his blood pressure was 190/100 mm. Hg. His pulse was irregular, varying in rate from 150 to 110 per minute; respiratory rate was 26 per minute and his temperature, 98° F. He appeared cyanotic and had a contusion of the vertex of the skull. The heart was enlarged. He appeared lethargic but, on awakening, was well oriented for time and place and able to follow simple commands. His right eye was abducted. On left lateral gaze, one noted nystagmus of the left eye, but there was no adduction of the right eye. Lateral gaze to the right revealed no abnormalities. There was limitation of upward gaze with nystagmus of both eyes. Downward gaze was normal. There was a left lower facial weakness. He exhibited a left hemiplegia with increased muscle tone, increased deep tendon reflexes, and Babinski sign. Sensory examination revealed no abnormality. Routine laboratory examinations demonstrated the blood urea nitrogen to be 61 mg. per cent but were otherwise normal. The electroencephalogram revealed bilateral diffuse slow waves with high to moderate voltage electrical activity, more marked on the right. The patient remained essentially unchanged until Feb. 12, when he was found with his eyes open but totally unable to communicate with the examiner in response to verbal or written commands. He kept his eyes open for long periods, but, when closed, the eyes opened promptly in response to a loud sound or painful stimulus. There were no spontaneous movements, except for the eyes. An occasional feeble movement of the right extremities was elicited by painful stimulation. His akinesia and mutism persisted until shortly before death on April 2, complete coma being observed agonally.

Autopsy revealed pulmonary edema, bronchopneumonia, and bilateral empyema. There was a severe generalized and cerebral arteriosclerosis. A series of old infarcts in the left inferior frontal gyrus and in the corpus striatum bilaterally was observed. There was evidence of complete ascending degeneration of the left medial lemniscus from the medulla up to the upper midbrain. A small old infarct was present in the base of the pons on the right. The medulla showed 2 old infarcts; one had destroyed the left pyramidal tract, the

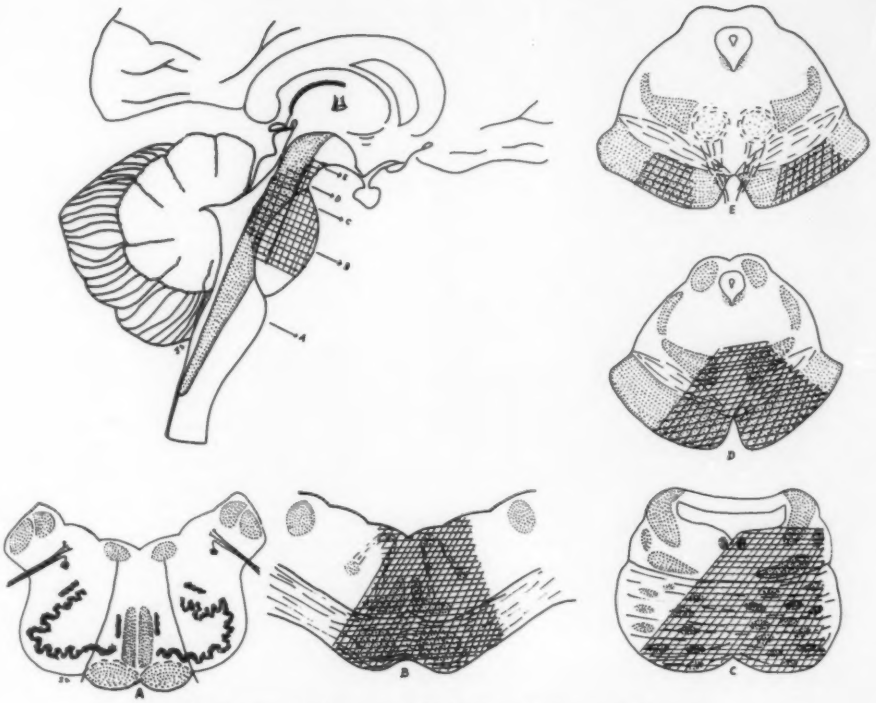

Fig. 8. *Case 7.* Diagram of distribution of lesions in brain stem

left medial lemniscus, and the left medial longitudinal fasciculus, and the other, a much smaller infarct, had destroyed part of the right fifth nerve nucleus and trigeminal tracts and the right spinothalamic and rubrospinal tracts. The spinal cord showed degeneration of the right crossed pyramidal and left direct pyramidal tracts. The cerebellum was normal (Fig. 7).

Case 7. This 67-year-old man was admitted to the hospital on March 28, 1957, with a history of repeated "small strokes" characterized by stupor, occasional difficulties in speech, and alternating transitory paralysis of 1 side of the body for a period of three years. A persistent left hemiparesis was known to have been present for one year. The patient was admitted to the hospital because of right hemiparesis and aphasia that started one day earlier. On examination, his blood pressure was 146/80 mm. Hg; pulse rate, 109 per minute; respiratory rate, 44 per minute; and temperature, 102° F. He was slightly cyanotic with signs and symptoms of pulmonary infection. He appeared motionless, lying in bed with his eyes open, sometimes moving them in all directions, although they were kept in the midposition for long periods of time. Occasionally, when his eyes were closed, he would open them in response to auditory stimuli or to painful stimuli on the right side of his body. In the latter circumstance, feeble movements of the stimulated right limb were sometimes observed. Painful stimulation elsewhere evoked no response nor did verbal or written commands to move or close his eyes. There were generalized increased deep tendon reflexes with bilateral Babinski signs. The laboratory examinations revealed a white blood count of 15,000 with 90% polymorphonuclear leukocytes and 10% lymphocytes. The cerebrospinal fluid was under normal pressure and contained 86 mg. per cent of total protein. Skull and chest films were normal. He remained essentially unchanged for eight to nine days, when his temperature rose to 105° F. and deep coma supervened; he died on April 10.

Autopsy revealed phlebothrombosis of the right iliac vein, bilateral pulmonary thromboemboli, lobular pneumonia, and thrombosis of the left subclavian artery. There was a marked cerebral arteriosclerosis with recent thrombosis of the basilar artery. Multiple old infarcts were noted in the cerebrum, involving the left superior parietal lobule and the right middle frontal gyrus, and a large

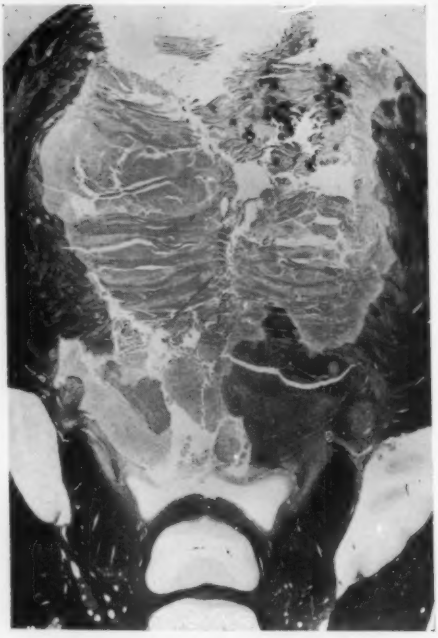

Fig. 9. *Case 7.* Pons, revealing extensive lesion in base and tegmentum. Mahon stain. × 5

recent infarct was found in the pons. The latter involved most of the base and a large portion of the tegmentum and extended upward to involve both cerebral peduncles. The medulla was not involved. The cerebellum revealed very early homogenizing necrosis of the Purkinje cells in some areas (Figs. 8 and 9).

Case 8. This 57-year-old woman was admitted to the hospital on Nov. 7, 1957, after having been exposed for twenty-two hours to illuminating gas (natural gas). On admission, the blood pressure was 100/0 mm. Hg; the pulse rate, 100 per minute; respiratory rate, 26 per minute; and temperature, 98° F. The eyes were kept closed and, when opened passively, did not move. The pupils were dilated and responded sluggishly to light. She was completely unresponsive, except for episodes of generalized rigidity when painfully stimulated. Muscle tone was diffusely increased, the deep tendon reflexes were hyperactive, and bilateral Babinski signs were elicited. The abdominal reflexes were absent. Routine laboratory examination of blood, urine, and cerebrospinal fluids revealed no abnormalities. Chest and skull films were normal. Three days after admission, she began to move her eyelids, and movements of the eyes wandering in an uncoordinated fashion were observed. One day later, her eyes began to remain open, to move coordinately in all directions, and to react well to light. The eyes would open promptly in response to painful or auditory stimuli. At times, in addition to opening her eyes, she moved the stimulated limb slightly or revealed decerebrate movements. The gag reflex was present from the sixth day after admission until death, permitting feeding by mouth. There was no observable change in the akinetic state until the twenty-third hospital day, when one observer thought that the patient would squeeze his hand feebly on command. Efforts by others to elicit a consistent movement of the eyes or any other response by visual or auditory commands were not successful at any time during her hospitalization. The electroencephalogram at this time showed diffuse dysfunction, with slow waves of high to moderate voltage electrical activity bilaterally. During the following week, electroshock therapy was given on 10 occasions, without effect, because of an interpretation that the akinesia and mutism might represent a catatonic state. The akinetic mutism remained unchanged until death on Jan. 20, 1958, which was caused by urinary infection and shock.

Autopsy revealed chronic cystitis and thromboemboli in the pulmonary artery. There were extensive cystic infarcts in the globus pallidus bilaterally and a similar cystic infarct in the right middle frontal gyrus anteriorly, measuring 2 to 3 cm. in maximal diameter. Microscopically, there was a diffuse, moderately severe neuronal loss, most evident in the frontal cortex. The thalamus, hypothalamus, midbrain, pons, medulla, and cerebellum appeared normal (Fig. 10).

DISCUSSION

The 8 patients described all revealed the syndrome of akinetic mutism in that they appeared immobile, mute, and generally unresponsive, except with respect to their eyes. The eyes were generally kept open and moved

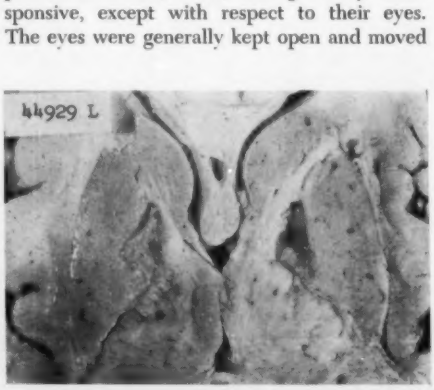

Fig. 10. *Case 8.* Bilaterally symmetric destructive lesions in globus pallidus. × 2

in all directions, apparently at random. The eyes were sometimes closed for short periods, particularly at night. They opened promptly in response to auditory or painful mechanical stimuli. The movements of the eyes were such that, at times, the observer was led to believe that the patient was aware of his presence and would follow him about the room. However, the patients would not respond consistently to a visual or auditory command to move the eyes in any given direction or to close them, although these motor activities were possible, being performed spontaneously at random, and the sensory pathways utilized were intact. This altered state of consciousness varied somewhat in depth. At times, some of these patients would move an extremity in response to painful mechanical stimuli, while, terminally, deep coma usually preceded death. Electroencephalographic examinations were performed in 3 of these patients, being normal in 1 (Case 5) and abnormal, with diffuse slow waves of moderate to high voltage electrical activity, in 2 (Cases 6 and 8).

In 7 of these 8 cases, the basic pathologic process was thrombosis of the basilar artery, with infarction of the brain stem and, in some instances, other areas as well. These patients lived for one to forty-eight days after the initial vascular insult. In 3 cases, the lesions were limited to the brain stem. In 2 others, there were, in addition, bilateral lesions in the occipital lobes and in the cerebellum, which antedated the brain stem lesions, and 1 of these revealed a fresh infarct in the subthalamus as well. The other 2 cases revealed, in addition to the infarcts in the brain stem, infarcts in the distribution of the carotid system; these latter lesions antedated the brain stem lesions in 1 instance and were of the same age in the other. The medulla oblongata was involved only in Case 6. The base of the pons was affected in all 7 cases, the destruction involving more than half of its cross-sectional area in 6 instances and a very much smaller proportion in the seventh. These estimates are based on representative sections, not on reconstructions of serial sections. The tegmentum of the pons was involved in all 7 cases. In 3 of these, the destruction is estimated as affecting over 50% of its cross-sectional area, while in the other 4, the involvement was much less extensive. The portion of the tegmentum destroyed was generally the ventromedial area. The tegmentum of the midbrain was involved in 4 cases; in 1 of these, there was in addition a unilateral involvement of the cerebral peduncle and, in another, bilateral peduncular lesions. In a fifth case, the tegmentum of the midbrain was not involved but there was a bilateral destruction of the peduncles.

The eighth case was that of a woman who survived eighty-one days after illuminating gas poisoning. The abnormality in her state of consciousness was exactly like that in the other 7 cases. Pathologically, the brain revealed grossly evident lesions in the globus pallidus bilaterally and a small lesion approximately 3 cm. in diameter in the right middle frontal gyrus anteriorly. These lesions were cystic and resembled infarcts of an age consistent with the duration of symptoms. In addition, a neuronal loss was clearly apparent microscopically in the cortex of both frontal lobes. Neuronal loss was probably present in other regions of the brain as well, but the intensity of neuronal change was less than could be evaluated by our technics. The thalamus, subthalamus, hypothalamus, brain stem, and cerebellum appeared normal.

Although the lesions in Case 8 differed so strikingly from those observed in the first 7 cases, the altered state of consciousness appeared the same. Indeed, the same alteration in consciousness has been observed in association with bilateral cingulate gyrus destruction,[3–6] bilateral thalamic hemorrhage,[2] pineal tumors,[2] craniopharyngeomas, and epidermoid cysts, particularly those extending into the third ventricle;[2] in cerebellar and other posterior fossa tumors;[7,12] and after operative procedures to relieve hydrocephalus.[2] It is evident that akinetic mutism is not simply the reflection of the destruction of sensory pathways, nor can the immobility observed in these cases be due simply to a destruction of the motor pathways. Indeed, at first glance, it seems quite difficult to recognize any one mechanism that may be applicable to all these varied cases.

Our own experience suggests that the single most common area of destruction is the brain stem. The relationship of the reticular forma-

tion in the brain stem, and in other areas, to altered states of consciousness has been documented in great detail,[13–30] and it is very probable that this relationship may be directly involved in the first 7 cases described in the present paper. The same may be true with respect to the cases of akinetic mutism and other forms of altered consciousness associated with posterior fossa tumors compressing the brain stem[7,12,17,18] and with lesions about the third ventricle, which press upon the thalamus, hypothalamus, subthalamus, and upper brain stem,[2,31] since these structures represent the rostral portion of the reticular activating system. It has been stated that the cingulate gyrus has direct and intimate connections with the medial reticular formation of the pons[32–34] and that this latter area supresses all muscular action.[35] Interruption of this connection at the cortical level may account for the akinetic mutism observed in some instances of bilateral destruction of the cingulate gyri.[3–6,36] In our eighth case, that due to gas poisoning, a specific relationship to changes in the reticular activating system can be postulated, at least to the extent that the neurons within the reticular substance shared the anoxic injury. Actually, such efforts to implicate the reticular activating system in each of these situations appears strained, particularly when one recalls the number of instances in which pathologic findings like those seen in the cases of akinetic mutism cited are found in its absence.

We cannot fail to be impressed by our own experience, which relates akinetic mutism in 7 of the 8 cases in which it was observed to disease of the brain stem. When we compare these 7 cases of basilar artery thrombosis, in which akinetic mutism was observed, with the 15 cases of basilar artery thrombosis, in which deep coma had been observed, studied in this laboratory in the same period, the major distinction proved to be the greater degree of involvement of the tegmentum of the brain stem in the latter group. It may be well to look upon these alterations in the state of consciousness as a continuous spectrum of change varying from a state of deep, completely unreactive coma through a state of akinetic mutism, a state of stupor, and, finally, full wakefulness.

While patients in a state of akinetic mutism may appear to be aware of their surroundings, it is probable that this is not the case. At least, such awareness could not be demonstrated in our 8 cases. Although the patients could move their eyes and respond to an auditory stimulus, by opening them, and the visual pathways appeared morphologically intact, an intellectual, visual, or auditory command, such as "close your eyes" or "move your eyes to the right," elicited no response. A similar lack of awareness is likely in Cairns' case.[2] His patient, after recovery from a state of akinetic mutism, had no recollection of the events that occurred during this state. In those catatonic schizophrenic states that simulate akinetic mutism, there is awarness, since these patients do have memory of the events happening during the catatonic state.

In the light of the experimental evidence of the activity of the reticular activating system as an alerting mechanism for the cerebral cortex, it is possible that its partial destruction might be accompanied by such disturbances in awareness as those seen in akinetic mutism. As a result of the partial destruction of the reticular formation, the reticular activating system may energize the neural activity derived from external or internal stimuli to a degree sufficient to maintain the movements of the eyes and the slight reactivity described but not sufficient to maintain a degree of awareness permitting an intellectual command to be understood and carried out.

SUMMARY

An altered state of consciousness, akinetic mutism, was observed in 8 persons. They appeared motionless and speechless, as if in coma, but their eyes remained open for long periods, moving in all directions. Auditory and painful stimuli caused prompt opening of their eyes, and painful stimuli occasionally induced a withdrawal reaction. Although they seemed aware of their surroundings, communication through visual and auditory commands could not be established.

Autopsy disclosed, in 7 cases, obstruction of the vertebral-basilar system with infarcts in the brain stem, including portions of the reticular substance. In the eighth patient, who died of carbon monoxide poisoning, ex-

tensive neuronal damage in the cerebral cortex and bilateral pallidal encephalomalacia were present.

It is suggested that akinetic mutism resulted from the partial destruction of the reticular activating system in the brain stem in the 7 cases of basilar artery thrombosis. The mechanisms involved in the eighth case and in a heterogeneous group of cases of akinetic mutism described in the literature remain obscure but may possibly reflect disturbances of the reticular activating system at other levels.

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Dissecting aneurysms of intracranial arteries

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DISSECTING ANEURYSMS of intracranial arteries are rarer than those of the aorta and other peripheral vessels, only 15 cases having been reported.[1-14] Bigelow[12] reviewed 10 of these in 1955; 3 cases in the foreign literature were not included,[1,3,6] and 2 cases were reported later.[13,14] As he pointed out, instances of this disease probably have been overlooked in the presence of associated cerebral thrombosis with infarction or hemorrhage. An interesting aspect of this condition is the diversity of predisposing factors and causes, which include trauma, electrocution, syphilis, arteriosclerosis, heatstroke, and migraine. The following case occurred as a complication of tonsillectomy.

CASE REPORT

The patient, a 29-year-old white woman, had tonsillectomy under local anesthesia for chronic tonsillitis. Slight bleeding from the tonsillar fossa one hour later was controlled with hot saline irrigation and injections of 75 mg. of vitamin K and 5 mg. of Adrenosem salicylate. Two hours after surgery, she was restless and required ¼ gr. of morphine for pain. Urticaria developed and was treated with 30 mg. of Benadryl. The bleeding recurred, and the patient became stuporous. Ligatures were applied to the fossa under 0.25-gm. Pentothal anesthesia four hours after the tonsillectomy; a transient drop in blood pressure to 88/40 mm. Hg was noted at this time. She did not become fully responsive after this procedure. The following morning, she was found to have hemiparesis, facial weakness, hyperactive deep tendon reflexes, and an extensor plantar reflex, all on the left side. She was unable to speak but could write. The spinal fluid showed no abnormalities. She became febrile, remained semicomatose, and required parenteral feeding.

The patient was brought to Colorado General Hospital on the third postoperative day in a stupor, aimlessly threshing her right arm and leg and responding only to painful stimuli. Her head was turned to the left, and rotation to the right caused pain. Nuchal rigidity was absent. Papilledema, mainly on the right, left facial paresis, diminution of the left corneal reflex, left flaccid hemiparesis, and brisk equal deep tendon reflexes were present. The common carotid and temporal arterial pulsations were normal. A left hemisensory defect could not be evaluated fully.

An arteriogram showed that the right internal carotid artery was patent to the level of the bifurcation of the anterior and middle cerebral arteries, where an obstruction was demonstrated (Fig. 1). The blockage was abrupt, and the dye terminated as a serrated rosette-like opacity. The patient received oxygen and intravenous fluids. Hypertonic glucose solution was injected to reduce the increasing intracranial pressure. In spite of these measures, her sensorium became progressively obtunded and twitching of the right arm developed. She was completely flaccid and unresponsive, with periodic respirations and rising temperature and pulse rate; she died on the sixth postoperative day.

Autopsy. The body was that of a normally developed, somewhat obese white woman. Minimal subcutaneous hemorrhage was noted about a needle puncture mark located 6 cm. inferior to the angle of the right mandible. The internal carotid arteries in the neck did

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Fig. 1. Arteriogram showing rosette-like termination of column of dye at the point of bifurcation of the anterior and middle cerebral arteries

Fig. 2. Right anterior cerebral artery showing extreme dissection and intramural hematoma with total obstruction of lumen (Elastic fiber-Van Gieson stain × 35)

not exhibit intimal lesions or mural hemorrhage. The tonsillar fossae were covered with shaggy brown clot. Gross findings otherwise were limited to the cranial contents. The embalmed brain weighed 1,300 gm. The meninges were normal and free from hemorrhage. The right internal carotid, middle cerebral, and anterior cerebral arteries were thin-walled and distended with soft, red blood clot. The right frontal, parietal, and temporal lobes and basal nuclei were swollen and slightly softened without liquefaction or hemorrhage. There was uncal herniation.

Microscopically, the internal elastic membrane of the right middle cerebral artery exhibited diffuse homogeneous thickening with splitting and foci of thinning. The elastica was extensively detached from the media in the major vessels and, at some levels, was anchored only at 1 or 2 points (Fig. 2). Unclotted blood and some coagulated fibrin filled the false lumen and collapsed the original channel. In some places, the detached elastica floated in the lumen and the hematoma was absent (Fig. 3). The media itself was normal in most places, and smooth muscle fibers rarely accompanied the elastica in its displacement (Fig. 4). Medial necrosis and adventitial changes were not observed. The intima was

Fig. 3. Right middle cerebral artery showing extensive detachment of internal elastica (Elastic fiber-Van Gieson stain × 25)

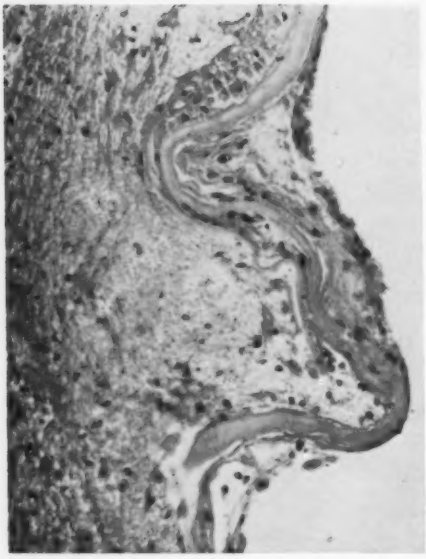

Fig. 4. Detached inner coats of right middle cerebral artery showing slight intimal fibrosis, prominent irregular thickening of internal elastica, a few medial muscular fibers at top, and underlying thrombus (Hematoxylin and eosin × 185)

thin and seemingly intact throughout, with only an occasional small patch of fibrosis. The other cerebral arteries were normal, showing at most a mild to moderate generalized thickening of the internal elastic membrane. The Sudan black, periodic acid-Schiff, alcian blue, and toluidine blue stains were applied to sections of the involved vessels. Lipoids, abnormal amounts of periodic acid-Schiff positive material, and metachromatic substances were not present. The aorta, cervical portion of the right internal carotid artery, and other systemic vessels were also examined with these stains and with the Verhoeff stain for elastic tissue, and abnormalities were not demonstrated.

DISCUSSION

That the dissection originated in the internal carotid artery at the bifurcation of the middle and anterior cerebral arteries and progressed peripherally was apparent from the arteriogram. Evidence of preexisting arterial disease, such as medial necrosis, was absent. The internal elastic membrane was decidedly swollen and was discretely elevated from the media, carrying only rare muscle fibers with it. The significance of this finding was debatable, since splitting and collagenosis of the internal elastica appears in arteries of various calibers, even in very early life. While this change in the arteries involved was more marked than usual and may have predisposed to the detachment of the membrane, it still was not severe and may have developed, at least in part, during the several days before death. A small tear in the intima was assumed to be the initial site of the dissection, although it was not demonstrated.

Incidentally, this lesion is termed dissecting aneurysm only because most of the cases in the literature are so labeled. The term dissecting intramural hematoma is preferred. Blood penetrates the wall of the vessel, causing a split along the natural lines of cleavage without necessarily increasing the external diameter of the artery.

A great variety of seemingly unrelated predisposing conditions has been associated with this disease, as is shown in the appendix. Luetic vasculitis was significant in 2 cases, arteriosclerosis with degeneration of the media in 3, trauma in 3, and electrocution, migraine, and heatstroke in 1 each; 4 cases appeared to be "idiopathic." Of the reported cases, 8 occurred in males and 4 in females; the sex was not stated in 3. The age of the patients ranged from 6 months to 47 years; the age was not stated in 3. Any one or more of the principal arteries may be involved. The clinical findings in all cases were appropriate to occlusion of the affected vessel; nothing was noted to distinguish them from commonplace thrombosis or hemorrhage. The onset was acute, and the period of survival usually varied from one to seventeen days; 2 patients survived with surgery.[10] The duration was not cited in 5 cases. A unique case of spontaneous healing of a middle cerebral arterial dissecting aneurysm was described by Norman and Urich.[14] Following a sudden hemiplegia, an infant had convulsions and failed to develop mentally, dying fourteen years later with tuberculosis. Communications between the false

and original lumens of the vessel were demonstrated.

Several of the theories of pathogenesis of dissecting hematomas may be excluded in this case. The lesion was not related to the introduction of a needle into the carotid artery for the arteriogram.[15] Primary involvement of the outer coats of the vessel with inflammation leading to dissection within the media was absent. Such a mechanism was considered to be important by Aronheim and Wagman[16] in a case of intramural coronary arterial hemorrhage. Medial necrosis, which appears to be the principal factor in dissecting aneurysm of the aorta, also was absent. It is noteworthy that, in extracranial arteries, the plane of cleavage lies within the media or between the media and adventitia, while, in cerebral vessels, it develops between the internal elastic membrane and the media. Mucoid degeneration of the media associated with arteriosclerosis was observed in only 2 cases with intracranial lesions. The mechanism of intramural hematoma formation described by Paterson,[17] consisting of rupture of capillaries within sclerotic intima which were derived from the main arterial lumen, clearly did not play a role in this case.

REPORTED CASES OF DISSECTING ANEURYSMS OF INTRACRANIAL ARTERIES

Case 1. Turnbull, 1915.[1] A case of considerable hemorrhage due to rupture of dissecting aneurysm of right middle cerebral artery, at site of acute syphilitic arteritis.

Case 2. Scholefield, 1924.[2] Male, 47 years. Death fifteen days after onset of "cold" with symptoms of softening of brain stem. Dissecting aneurysm of right vertebral and basilar arteries.

Case 3. Stern, 1933.[3] Male, 24 years. Death six days after developing coma following heatstroke incurred on a forced march. Dissecting aneurysm of basilar, posterior cerebral, posterior communicating, and anterior choroidal arteries.

Case 4. Hyland, 1933.[4] Male, 42 years. Death seventeen days after onset of headache and left hemiplegia. Dissecting aneurysm of basilar artery which exhibited mucoid medial degeneration and necrosis.

Case 5. Hassin, 1937.[5] Male, 37 years. Accidental electrocution. Torn and detached internal elastic membrane of larger arteries, especially the basilar.

Case 6. Szabó, 1939.[6] Female, 35 years. Softening of brain stem produced by dissecting aneurysm of right vertebral artery associated with syphilitic mesarteritis.

Case 7. de Veer and Browder, 1942.[7] Male, 42 years. Death fifty-seven hours after trauma to head. Separation of intima and internal elastica from media of right middle cerebral artery.

Case 8. Dratz and Woodhall, 1947.[8] Female, 21 years. Death second day after bicycle-auto accident. Extensive dissecting aneurysm of left internal carotid and adjoining anterior and middle cerebral arteries.

Case 9. Ramsey and Mosquera, 1948.[9] Male, 47 years. Unconsciousness and left hemiparesis after two weeks of occipital headache, with death on sixth day. Massive subarachnoid hemorrhage from dissecting aneurysm of right middle cerebral artery, which showed cystic medial degeneration and severe arteriosclerosis.

Case 10. Poppen, 1951.[10] Patient recovered after resection of dissecting aneurysm of angular branch of middle cerebral artery, which was demonstrated by angiography.

Case 11. Poppen, 1951.[10] Patient well eight years after ligation of internal carotid artery for dissecting aneurysm of medial trunk of middle cerebral artery, demonstrated by angiography.

Case 12. Sinclair, 1953.[11] Female, 27 years. Severe migraine for several years. Death on fourth day after left hemiplegia during an attack. Dissecting aneurysm of right middle cerebral artery; degeneration or inflammation absent.

Case 13. Bigelow, 1955.[12] Female, 46 years. Death one day after excision of berry aneurysm of right middle cerebral artery, from postoperative dissecting aneurysm of the same vessel.

Case 14. Watson, 1956.[13] Male, 32 years. Death fourth day after symptoms of pontine hemorrhage. Dissecting aneurysm of basilar artery associated with medial degeneration.

Case 15. Norman and Urich, 1957.[14] Male, 14 years. At age 6 months, sudden hemiplegia followed by convulsions and arrest of mental development. Died of pulmonary tuberculosis. Dissecting aneurysm of right middle cerebral artery and its main branches; healing with endothelium lining the false lumen that communicated with the main lumen both proximally and distally.

The factors that appear to be most important in the pathogenesis of dissecting intracranial hematomas are the peculiar anatomy of the cerebral arteries, the traumatic influence of severe fluctuations of the blood pressure, previous disease of the vessel wall, and external violence. Structural differences between the systemic and cerebral arteries have long been appreciated. The latter are normally thinner, more fragile, and less well supported and lack an external elastic membrane. Triepel[18] and others have described the relative prominence of the internal elastic membrane, the paucity of elastic fibers in the media, and the thinness of the adventitia. Forbus[19] clearly demonstrated congenital defects of the media at the arterial bifurcations and degenerative gaps in the elastica as well. Carmichael[20] also found that circumscribed areas of complete deficiency in the muscular coats of the larger arteries are a frequent occurrence due to defective development and that similar defects in the internal elastica result from erosions or degeneration due to atheromas. The significance of these defects in the arterial coats have been considered by many authors in the pathogenesis of cerebral aneurysms. Glynn[21] noted such medial discontinuities in 80% of both aneurysmal vessels and controls but felt that the changes in the internal elastic membrane were more important. Richardson and Hyland[22] also believed that acquired degenerative lesions of the elastica, in addition to the medial defects, played a part in the formation of cerebral aneurysms. Walker and Allegre[23] stated that intimal and elastic tissue changes in aneurysms were related to the increased stress because of the absence of an external elastic membrane. Forster and Alpers[24] concluded that the medial defects were congenital in type and felt that the variable changes in the elastic membrane were secondary to the presence of the aneurysm. Although the importance of these vascular defects appears to be unsettled, their frequent occurrence is established. In our case, it seems plausible that a small congenitally weak intimal area tore with stress, admitting blood into the wall.

One of the principal factors in the pathogenesis of certain of the dissecting hematomas is the sudden increase and fluctuation of blood pressure. This was the sole acceptable explanation in Stern's case of heatstroke.[3] Such a functional vascular disturbance was most likely involved in Sinclair's case of migraine, since histologic abnormalities were absent.[11] Watson,[13] in reviewing 23 cases of dissecting aneurysms of arteries other than the aorta, found that hypertension, especially when acute, was a factor in 9. This was a significant incidence, since 5 were due to trauma and information was not available in 3 cases. In 2 other cases, severe exhaustion of the patients was important and blood pressure may have been altered. The case of Wegelin[25] was of interest in this connection; hypertension with eclampsia led to dissection of the inferior thyroid artery. Certainly, abnormal pressure changes were recorded in the present case, although a sudden elevation had not been charted.

It is interesting to speculate whether there may have been stretching or compression of the carotid artery during the tonsillectomy, as well as a vasomotor disturbance. Dratz and Woodhall[8] suggested that, in their case of head injury, movement of the brain within the skull created torsion and tension on the artery with tearing of the wall. We conclude that the 2 main factors are the peculiar structure of the internal elastic membrane and media and sudden fluctuations of blood pressure, with or without mechanical stress on the vessel.

Antemortem diagnosis may be made and successful surgical intervention achieved, as proved by the cases of Poppen.[10] In retrospect, the distinctive obstruction demonstrated by the arteriogram in this case would indicate operation, had the patient been seen immediately after the onset of symptoms. Early surgical treatment might be lifesaving by preventing the continuation of the dissection and development of parenchymal softening. Although this lesion is rare, it should be included in the differential diagnosis of cerebral vascular occlusions in relatively young patients in the absence of preexisting cardiovascular or cerebral disease.

SUMMARY

A 29-year-old woman developed hemiplegia after tonsillectomy. An obstruction at the bifurcation of the middle and anterior cerebral arteries was demonstrated by arteriogram. Death occurred on the sixth postoperative day. Fresh softening of the cerebral hemisphere was

due to dissection of the wall of the middle and anterior cerebral arteries, with detachment of the internal elastic membrane from the media and formation of intramural hematoma. The pathogenesis was discussed. Peculiarities in the structure of the cerebral arteries and sudden fluctuations of blood pressure with or without trauma to the vessels were believed to be essential factors; 15 cases of this disease were reviewed briefly.

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Dystrophia myotonica

A clinical and electromyographic study of the effects of certain drugs on myotonia

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DYSTROPHIA MYOTONICA is a heredofamilial disease characterized by a wide range of clinical manifestations, such as cataract, muscle atrophy, myotonia, gonadal atrophy, hyperostosis cranii, and congenital defects.

Previous studies suggest that the defect in functioning muscle is distal to the neuromuscular junction. Thus, blocking of the motor nerve[28] or brachial plexus[4] and spinal anesthesia failed to relieve myotonia. Also, blocking of the motor end plate with d-tubocurarine[7,8] failed to abolish myotonic response to mechanical stimulation. Earlier, Brown and Harvey,[3] in their experiments on myotonic goats, observed that neither administration of curare nor sectioning of the motor nerve abolished myotonia.

Work on muscle electrolytes by Cumings[6] and later by Blahd and associates[2] and Williams and associates[34] demonstrated that the potassium content of the dystrophic muscle was considerably decreased, while the sodium content was greater than normal,[34] thus showing that, in dystrophia myotonica, there is possibly a defect in muscle cell membrane permeability. This view was further supported by the work of Schapira, Dreyfus, and Schapira,[30] who found that aldolase content in myotonic muscle was decreased and the level of serum aldolase significantly increased, while Zierler[35] observed that increased permeability of the muscle membrane was associated with increased outflow of the aldolase from the muscle. The evidence therefore seems to suggest that, in dystrophia myotonica, there is some disorder of cell metabolism. There are then 2 possible ways in which drugs may improve myotonia. These are either by use of drugs which, among other effects, alter the membrane permeability of the cell or by use of drugs which affect cell metabolism. In this paper, we report studies on these 2 aspects.

METHODS

Full clinical and laboratory investigation of 6 patients with "fully developed" dystrophia myotonica was done in hospital. Electromyographic studies were done on the long flexor muscles of the fingers during a standard grip. The arm of the patient was postured with the elbow flexed at approximately 110°, and the wrist was in slight flexion in order to decrease the myotatic reflex. The skin was prepared by first rubbing it with ether and then applying an electrode jelly containing sodium chloride, pumice, starch, glycerine, and water. Care was taken to keep the skin resistance at 5 to 10 x 103 ohms; 3 lead suction electrodes, 1 cm. in outside diameter, were placed on the skin overlying the long flexor muscles 1 cm. apart. The leads from these were taken into an Ediswan 2-channel oscillograph, and calibrations were adjusted to give a deflection of 2 and 5 mm. for a standard input of 50 μv. Different amplifications were used in the hope of facilitating recognition of the end point of the myotonia, as described by Liversedge and Newman.[18] As will be noted, in patients with dystrophia myotonica we frequently encountered marked spontaneous activity. This made the determination of the end point very difficult in some cases, but we have endeavored to assess it after mutual discussion. The stated figures in those cases in which this difficulty arose must be accepted with this reservation in mind. Where the difficulty occurred, we will make it clear in the text. In other cases, the end point was quite clear and could be as-

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sessed with confidence. At command, the patient gripped, to the best of his ability, a folded cuff of a sphygmomanometer, which was inflated to 30 mm. Hg, for a period of 5 seconds and then relaxed without full extension of the fingers. Myograms were recorded at 5-minute intervals, and the average duration of the myotonia was calculated.

To exclude artifacts due to electric interference, some recordings from the patients were carried out in a screened room and the recording conditions were repeatedly checked by recording from a normal person immediately after.

ADMINISTRATION OF DRUGS

1. Quinine sulphate, 10 gr. three times daily, was administered for three days. Recording was done four hours after the last dose, when a high concentration of the drug in the blood could be expected.

2. Procaine amide, 1 gm., was given orally one hour before electromyography.

3. Glucose, 50 gm., was administered to a fasting patient and 0.1 unit of soluble insulin per kilogram of body weight was given intravenously 60 minutes later. Electromyograms were done every 5 minutes after the administration of insulin, for a period of one hour.

4. Adrenal steroids (glucocorticoids): Cortisone, 100 mg., or Ledercort (9 alpha-fluoro-16-hydroxyprednisolone), 4 mg., was given orally twelve hours before the electromyogram. Neher[23] suggested that increased glycogen deposition occurs at that time.

5. Glutamic acid, 15 gm., was given orally in a single dose one hour before the recording. Highest concentrations of this amino acid occur one hour after administration.[1] The level then falls to the initial level at the end of two hours. Recordings were taken one hour after administration and every 5 minutes thereafter for one hour.

6. M/6 sodium lactate, 20 cc., was given intravenously to a fasting subject 30 minutes after the oral glucose. Electromyograms were taken immediately after.

CASE RECORDS

Case 1. R.F., a single man aged 37 years, at 13 had noticed difficulty in relaxing his grasp and, two years later, muscular weakness. He became progressively weaker, and muscle wasting progressed. He now had difficulty in rising from the lying position and had a tendency to fall in the street.

Family history. His mother had bilateral lenticular opacities and myotonia, and a brother had fully developed dystrophia myotonica.

Examination. The patient was an obese man with frontal baldness and profuse facial and body hair. Numerous pigmented moles on his trunk and limbs and syndactyly of the toes on the left foot were noted. He had bilateral posterior polar cataracts, a myopathic facies, and a weak smile. Mechanical myotonia of the tongue was found. The anterior cervical and sternomastoid muscles were wasted and very weak. Neck extension was strong. He was unable to sit up from the lying position with arms folded across his chest. The abductors of the arms were weak, and the biceps and triceps and the wrist and finger flexor and extensor muscles were wasted and weak. Marked active and mechanical myotonia of the thenar and hypothenar muscles was seen. He had pseudohypertrophy of the calves and thigh muscles and weakness of the ileopsoas and quadriceps muscles. Dorsiflexion of both feet was weak. All deep reflexes were absent.

Investigation. The skull x-ray showed a thickening of the whole calvarium and hyperostosis frontalis. Basal metabolic rate was —21% and —19%. 17-ketosteroids were 6.9 mg. in twenty-four hours. The electrocardiogram was normal. The glucose tolerance test done on arterial blood showed some resistance, with a failure to return to a fasting level in two hours. (75—125—140—110 mg. per cent).

Electromyography. Control study without drugs of a standard grip showed myotonia lasting 5.8 seconds; there was no spontaneous activity, and, hence, the assessment of the end point was reliable. After 10 gr. of quinine sulphate three times daily for two days, the myotonia persisted for 1.8 seconds. After 1 gm. of procaine amide given an hour before recording, the myotonia persisted 0.8 seconds. After 100 mg. of cortisone taken twelve hours before recording, duration was 1.3 seconds. Glucose (50 gm.) and insulin (7.5 units) intravenously caused a marked decrease of the myotonia, within 20 minutes after administration, to 2 seconds; this lasted for 20 minutes, and then there was gradual return within an hour to a myotonia lasting 8 seconds.

Case 2. A.F., a single man aged 42 years, noticed inability to relax his grip and progressive weakness of his limbs at 22. He became bald in his early 20's. Recently, he had had an increasing tendency to fall and on this account was unable to go out alone.

Family history. His mother had bilateral cataracts, a brother had fully developed dystrophia myotonica, and a sister had had 4 stillbirths.

Examination. The patient was a bald man with wasting of the temporalis muscles, a myopathic

facies, and mechanical myotonia of the tongue. The sternomastoid and anterior cervical muscles were very weak and the extensors, strong. Pseudohypertrophy of the deltoid muscles, wasting and weakness of the forearms, active myotonia of the grip, and mechanical myotonia of the thenar and hypothenar muscles of the hands were noted. He was unable to sit up with arms folded. Marked weakness of the thigh calves and dorsiflexor muscles of the feet and mechanical myotonia of the calf muscles were found. All deep reflexes were absent. The testicles were atrophic.

Investigations. The chest x-ray was normal. The skull showed increased thickness of the calvarium. Basal metabolic rate was 8%. The I^{131} uptake was normal. Serum lipids were 760 mg. per cent; serum sodium, 137 mEq.; and serum potassium, 5.9 mEq. Urinary excretion of potassium was 71.5 mEq. and of sodium, 192 mEq. in twenty-four hours; 17-ketosteroid excretion was 11.3 mg. The glucose tolerance test showed a flattened curve (55—57—100—55 mg. per cent. The electrocardiogram showed concaved elevation of the S-T segment over the left ventricle. The electroencephalogram showed generalized low voltage activity. Slit lamp examination showed bilateral lenticular opacities characteristic of dystrophia myotonica.

Electromyography. The control grip was weak—75 mm. Hg. The interpretation was difficult, since it was impossible to determine the end point of the myotonia after relaxation of a standard grip because of spontaneous electrical activity observed in the electromyogram. Our assessment of the myotonia after the control grip was 11 to 21.5 seconds. After 1 gm. of procaine amide one hour before recording, duration of the myotonia was 1.5 to 5 seconds. The continuous electrical activity, though persistent, was decreased, and there was considerable improvement clinically. After 10 gr. of quinine sulphate twice daily for three days, the power of the grip improved to 90 mm. Hg and relaxation time fell to 2 to 5.5 seconds. Electrical activity was greatly decreased in between the grips, but a few fibrillation potentials were noted and the patient was conscious of an occasional twitch in the muscle. When 100 mg. of cortisone was given twelve hours prior to recording, the continuous electrical activity was reduced and myotonia persisted 2 to 5 seconds (average 3.5 seconds). Glutamic acid, 15 gm., given 75 minutes before recording reduced the myotonia to 1.5 to 3 seconds, which lasted one hour; after this, there was a prolongation of myotonia to 9 to 11 seconds. Glucose, 50 gm., and 1/6 molar sodium lactate, 22 cc., intravenously showed myotonia of 3.8 seconds after one hour. Glucose, 50 gm., was given and, 45 minutes later, 5 units of soluble insulin intravenously. Within 5 minutes, the myotonia was reduced to 3 to 4.5 seconds, which persisted for 40 minutes and then returned to 8 seconds.

Case 3. J.E.M., a married woman aged 57, noticed weakness of her limbs, difficulty in rising from the sitting or lying position, and a tendency to unexpected falls ten years before admission. The weakness increased gradually, and wasting developed. Her vision deteriorated soon after onset, and cataracts developed, one of which was removed from the left eye in 1955. A thyroidectomy was done in 1940.

Family history. There was no history of cataract or muscle dystrophy in her own family. An only son was examined and showed no evidence of dystrophia myotonica. The patient had had 3 miscarriages. The menopause developed at 50.

Examination. The patient was a middle-aged, obese woman with a myopathic facies. The skin was dry and had multiple pigmented moles. The hair was dry and lacked luster; the eyebrows were thin. There was some puffiness of the eyelids. The voice was hoarse. There was a hard nodule in the right lobe of the thyroid gland. The heart was normal; blood pressure was 130/90. A mature cataract was seen in the right eye. The facial muscles were weak. The sternomastoid muscles and anterior flexors of the neck were very wasted and weak. The neck extension muscles were weak; abduction of each arm was weak, but adduction was strong. Extension of the wrists and fingers was weak. Flexion was stronger. Marked active myotonia of the grip and mechanical myotonia of the tongue, thenar, and hypothenar muscles were noted. She was unable to sit up from the lying position or to lift her head from the pillows. The ileopsoas and quadriceps muscles were very weak. The hamstring muscles were strong. Dorsiflexion of the feet was weak, but plantar flexion was quite strong. All deep reflexes were absent.

Investigations. X-ray of the skull revealed increased thickness of the cranial vault; the pituitary fossa was normal. Chest x-ray revealed a large, calcified mass to the right of the trachea, which was thought to be a remaining portion of the thyroid gland. The electroencephalogram showed some generalized low voltage fast activity but was otherwise normal. The electrocardiogram showed an intraventricular conduction defect, the QRS complex being 0.14 second. B.M.R. was —7% and +3%. The I^{131} uptake was normal. A blood count was normal; total serum protein was 6.5%. The electrophoretic pattern revealed albumin, 54.3%; alpha globulin, 7.3%; alpha 2 globulin, 13.6%; beta globulin, 11.5%; gamma globulin, 13.3%; and serum lipids, 760 mg. The glucose tolerance test was 75—95—120—145 mg. per cent. The concurrent serum potassium levels were 5.4—5.2—5.3 mEq. The urinary 17-ketosteroids were 6 mg. in twenty-four hours.

Electromyography. Grip of the sphygmomanometer inflated to 30 mm. Hg raised the mercury column to 60 mm. (R) and 70 mm. (L). The end point of the myotonia was difficult to judge in control tracing on account of the continuous electrical activity. Quinine sulphate, 10 gr. three times a day for forty-eight hours, reduced the continuous electrical activity, and the end point of the myotonia then became obvious. Myotonia persisted for 2 to 3 seconds. The action potentials after

quinine were improved. After 1 gm. of procaine amide, the myotonia persisted 4 seconds. After 4 mg. of Ledercort in twelve hours, there was marked reduction of the continuous activity and the myotonia fell to 1.5 seconds. Forty minutes after insulin, the myotonia was reduced 3.2 seconds and this persisted for 35 minutes.

Case 4. L.F., a married woman aged 65 years, the mother of Cases 1 and 2, was admitted to the Dunedin Hospital on account of bronchitis. She had had dystrophia myotonica for several years. She was in heart failure with congestion and was treated with 2 gr. of digitalis daily and mersalyl injections twice weekly. At least 2 out of her 11 children suffered with the fully developed disorder. There was no history of cataract in the family.

Examination. The patient was an obese, middle-aged woman with bilateral ptosis and a myopathic facies. She had bilateral lenticular opacities and mechanical myotonia of the tongue. The thyroid gland was diffusely enlarged. Marked weakness of the neck flexors and the sternomastoid muscles was noted; the neck extensors were strong. There was wasting and weakness of the arms, most marked in the abductors of the shoulders, the biceps and triceps muscles and the flexors of the wrists and fingers. Active myotonia of the grip and mechanical myotonia of the thenar and hypothenar muscles of the hands were seen. The patient was unable to sit up from the lying position with her arms folded. There was syndactyly of the second and third toes of both feet. The dorsiflexors of the feet were very weak, and the deep reflexes were reduced and equal.

Investigations. The blood screen was normal. The skull x-ray showed moderate hyperostosis frontalis interna. Screening of the chest showed a limited excursion of the left half of the diaphragm. The vital capacity was 1,800 cc. Total nonprotein nitrogen was 38 mg. per cent. In the water excretion test, 50% of the water load was excreted in four hours. B.M.R. was +18%. The glucose tolerance test showed decreased tolerance (85—125—120—115 mg. per cent). Concurrent serum potassium levels were 5.5—5.4—5.3—5.2 mEq. The electrocardiogram was normal; the PR interval was 0.18 to 0.2 seconds.

Electromyography. The control myogram grip elevated the mercury to 80 mm.; there was continuous electrical activity, and it was difficult to define the end point of the myotonia. After 10 gr. of quinine sulphate three times a day for three days, the end point was definite and the myotonia fell to 1.6 to 3 seconds.

The patient had been taking 2 gr. of digitalis daily for her heart condition and, on the day the glucose and insulin test was done, showed some signs of digitalis intoxication—nausea and vomiting. The myotonia on that day was marked and persisted for 11 seconds. After glucose and insulin, myotonia was reduced to 3 to 6 seconds and persisted on this level for an hour before returning to its normal level. There was clinical improvement in the patient during the test; 100 mg. of cortisone reduced the myotonia to 1.5 seconds, and the power improved.

Case 5. W.C.H., a single man aged 30 years, had been an inmate of an institution for the feeble-minded since the age of 18. Dystrophia myotonica was first diagnosed at the age of 26. Recently, he had complained of exophthalmos, diplopia, and frequent dislocations of the jaw. No family history was available.

Examination. He was a young man with frontal baldness, a squint, hollowing of the temporal regions, ptosis of both lids, and a myopathic facies. Marked weakness and wasting of the sternomastoid muscles was found, but neck extension was strong. Pseudohypertrophy of the right biceps and left deltoid muscles was noted. Fasciculations were seen in the left deltoid muscle. The flexor and extensor muscles of the elbow and wrist and dorsiflexors of the feet were very weak. Mechanical myotonia of the tongue and hands and voluntary myotonia of the grip were seen. The abdominal muscles were weak.

Investigations. The basal metabolic rate was —8%; the I^{131} uptake was normal. Twenty-four-hour 17-ketosteroids were 20 mg. A glucose tolerance curve showed increased tolerance (0.055—0.090—0.090—0.055%), and concurrent serum potassium levels were 4.8—4.9—5.6 mEq. per liter. X-ray of the skull showed increased thickness of the vault. Radiologic examination of the cervical spine showed no abnormality. An electroencephalogram showed low voltage, 8.9 current strength activity mainly in right temporal region. Overbreathing produced increase of voltage and some low voltage 5 current strength in the occipital regions. An electrocardiogram showed changes in the S-T segment and an elevation of T waves. Slit lamp examination showed the presence of lenticular punctate opacities.

Electromyography. A control myogram of the grip of 120 mm. Hg showed myotonia lasting, on an average, 39 seconds with a clear end point. There were also spontaneous bursts of action potentials of 100 mv. of low frequency, sometimes lasting several seconds. After 1 gr. of procaine amide, the duration of the myotonia was 6.8 seconds (range, 4 to 11.5 seconds). There was also improvement of the power to 140 mm. Quinine sulphate decreased myotonia to 3.5 seconds. There was no change in power. Dilantin, 1½ gr. three times a day, produced some improvement of the grip, and myotonia lasted 11 seconds. Cortisone reduced myotonia to 4.8 seconds (range, 4.5 to 13 seconds). Glucose and insulin caused a decrease of myotonia within 10 minutes. Duration of the myotonia was 4 seconds for the next 50 minutes. High voltage single spikes were not abolished by any of the drugs used.

Case 6. Mr. McK., aged 58, married, has been investigated for the progressive increase of weakness in both arms and legs, present for fifteen

years. There was also some difficulty in chewing food. Recently, there was also loss of libido.

Family history. His parents were both healthy. A son had fully developed dystrophia myotonica, but 3 daughters were all well.

Examination. The patient looked older than his age, and his speech was slurred. There was marked frontal baldness, but hair was abundant elsewhere on the body. He had marked weakness of the facial muscles and ptosis of both eyes. The sternomastoids were very wasted and weak, but neck extensors were rather strong. In the arms, the deltoids showed some pseudohypertrophy but forearms and hands showed marked wasting. There was weakness of long flexors of the fingers, but wrist flexor and extensors were somewhat stronger. The grip was weak, and there was marked voluntary and mechanical myotonia. Abdominal muscles were very weak, and there was marked wasting and weakness of the quadriceps muscles in thighs and of the peroneal group of muscles in the legs. All deep reflexes were absent, but cutaneous reflexes were brisk. Laboratory investigations showed that hemoglobin was 13 gm.; erythrocyte sedimentation rate, 32 mm.; serum sodium, 136 mEq/l.; serum potassium, 5.1 mEq/l.; and total serum lipids, 1,260 mg. per cent. Glucose tolerance test was 60 mg. per cent fasting and, thereafter, 85—75—75 mg. per cent, while concurrent estimations of serum potassium were 5.2—4.8—3.9—3.9 mEq/l. Basal metabolic rate was —20%. An electrocardiogram showed PR interval of 0.28 seconds and elevated S-T segment in the lead one and AVL. X-ray of the skull showed marked thickening of the vault, and punctate cataracts were present in both eyes. Muscular biopsy showed marked variation in the size of the fibers, and there was marked formation of the nuclear chains. There was considerable increase of the interstitial tissue. Gonadal biopsy showed marked thickening of the lamina propria, but there was general decrease of the spermatogenesis. Leydig cells were seen but were not unduly prominent.

Electromyography. Grip was very weak on both sides, being 70 mm. Hg, and there was marked spontaneous electrical activity between the grips, making interpretation of the end point impossible. Administration of quinine and procaine amide was quite ineffective in reducing spontaneous activity, though periods of action potentials with lower amplitude were observed. There was no increase of power, and clinical improvement was slight. Following the administration of cortisone, the power increased to 80 mm. and the amplitude of the potentials in between the grips was somewhat decreased, but the end point of myotonia was not apparent at any time.

Glucose and insulin (6 units) reduced spontaneous activity within 10 minutes. The myotonia lasted at that time 3 seconds and was accompanied by a decrease of power to 60 mm. At the end of the test, with return of electrical activity, the pretest level power was 75 mm.

RESULTS

During these studies, it was found that, in the interpretation of the electromyograms, several factors had to be considered and the determination of an exact end point of the myotonia as it was described by Liversedge and Newman[18] was, in many instances, impossible.

The difficulties encountered could be placed in 2 groups.

1. Those due to external factors that were as far as possible controlled.

a. Cooperation of the patient, which is essential for this type of test, was easily obtained, and patients were eager to help; but, perhaps because of this, there was some tensing of muscles in the expectation of the command to grip, which was associated with the increased electrical activity.

b. Technic. It was hoped that by frequent checking of the electrode resistance and by prevention of desiccation of the jelly, there would be as little variation as possible.

c. The room temperature was usually 20 to 22° C., but it was noted that the hand holding the folded cuff tended to become cold because of the immobility and because of vascular disturbances often found in patients with dystrophia myotonica.

d. Extraneous electrical interference as stated above.

2. Those due to condition of muscle itself.

When the first 4 points were under adequate control, it was noted that the apparently relaxed muscles of patients in the required posture showed some spontaneous electrical activity that was not present in normal persons under the same conditions (Figs. 3 and 4).

The spontaneous electrical activity (Fig. 1) was present in 5 patients, and electrical silence in these patients could not be obtained, even when the recordings were done in a shielded room to exclude the possibility of outside interference. It also persisted with variable intensity throughout the control recording in between the grips and could be made worse by rubbing the skin. In 1 patient (Case 5—Fig. 2), bursts of single, large spikes of varying voltage and frequency were present on a background of spontaneous electrical activity. The presence of this spontaneous electrical activity made exact determination of the end point of myothonia in many instances impossible.

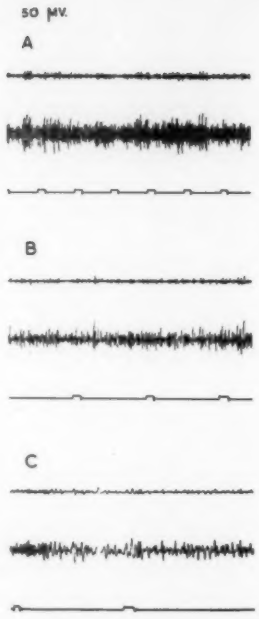

Fig. 1. *(Case 6)* Control electromyogram demonstrating presence of spontaneous electrical activity at rest. [A] Chart speed 1.5 cm. per second. [B] 3 cm. per second. [C] 6 cm. per second

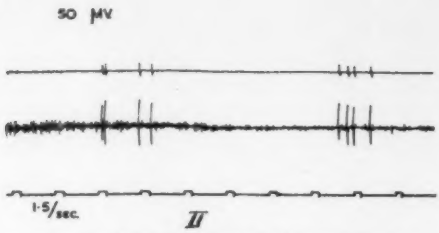

Fig. 2. *(Case 5)* Control electromyogram showing second type of the spontaneous activity: bursts of high voltage spikes (100 mv.)

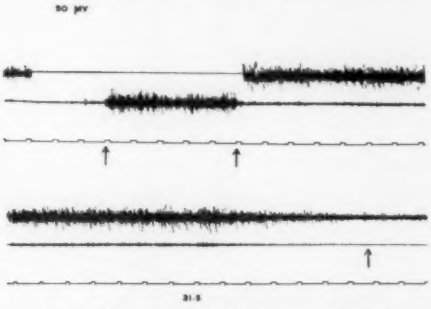

Fig. 3. *(Case 2)* Control electromyogram of 5-second grip. Duration of myotonia, 21½ seconds

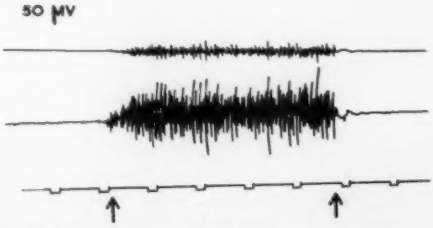

Fig. 4. Five-second grip in a normal person

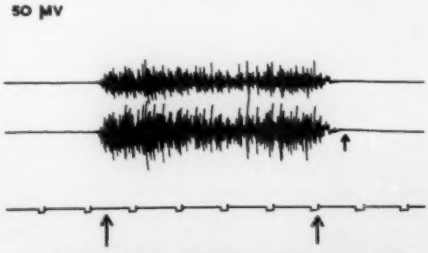

Fig. 5. *(Case 1)* Following administration of quinine sulphate; relaxation time, ½ second

As an indication of the duration of relaxation time, we considered the return of the amplitude of the potentials to the pregrip level. It was noted that this point usually coincided quite well with the clinical termination of myotonia in cases in which patients volunteered their subjective observation. Only in Case 1, in which the disease was less advanced, was the end point of myotonia sufficiently clear cut.

Results following the administration of drugs are set out in the table. Quinine sulphate (Fig. 5) was quite effective in reducing spontaneous electrical activity and also activity of the potentials during grip. It was possible to distinguish the end point of myotonia in 5 out of 6 patients, and the relaxation time was reduced.

In the sixth patient, quinine sulphate was without effect. It could be that there was

EFFECTS OF DRUGS ON MYOTONIA

Case	Control grip	Quinine sulphate	Procaine amide	Glucose and insulin	Gluco-corticoids	Glutamic acid	1/6 Sodium lactate
1. R.F.	5.8 sec.	1.8 sec.	0.8 sec.	2 sec.	1.3 sec.		
2. A.F.	20 sec. spontaneous activity	2–5.5 sec.	15–5 sec.	3–4.5 sec.	2–5 sec. (cortisone)	15–3 sec.	3.8 sec.
3. J.E.M.	Spontaneous activity	2–3 sec.	4 sec.	3.2 sec.	1.5 sec. (Ledercort)		
4. L.F.	Spontaneous activity	1.6–3 sec.		3–5 sec.	1.5 sec. (cortisone)		
5. W.C.H.	Spontaneous electrical activity 39 sec.	3.5 sec.	6.8 sec.	4 sec.	4.8 sec. (cortisone)	13.4 sec.	
6. J.McK.	Continuous electrical activity	Not effective	Not effective	3 sec.	Decrease of spontaneous activity		

Duration of myotonia shown in seconds

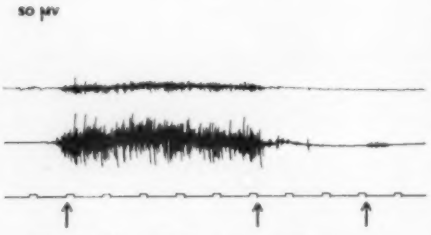

Fig. 6. *(Case 5)* Procaine amide was given one hour before recording. Relaxation time, 3 seconds

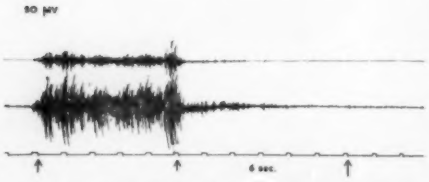

Fig. 7. *(Case 5)* Cortisone was given twelve hours previously. Relaxation time, 3 seconds

impaired absorption of the quinine from the gut, because, in the first case, in which quinine sulphate was ineffective, quinine bisulphate was effective. Also, the coating of the tablets might play a part, because it was found that quinine sulphate in capsules was more effective than in tablet form.

Procaine amide had a marked effect on the duration of the relaxation time and also on the muscle power (Fig. 6 and table). The relaxation time ranged between 0.8 and 6.8 seconds in Cases 1, 2, 3, and 5, and spontaneous electrical activity almost disappeared. There was also corresponding clinical improvement. In Case 6, though beneficial effect of the procaine amide was noticeable clinically, the electromyogram showed only prolongation of the periods of decreased electrical activity.

After the administration of glucocorticoids, the duration of myotonia was reduced in 5 patients (Fig. 7 and table) with almost complete disappearance of continuous electrical activity but the incidence of single spikes in Case 5 was unchanged. None of the patients were observed to be euphoric, though some of them volunteered spontaneously that they noticed increased ease of movements. There was no marked change in the electromyogram in Case 6, but a small decrease of spontaneous activity was observed.

Electromyograms made after administration of glucose and insulin showed decrease of myotonia and spontaneous activity, 20 to 40 minutes after insulin (Fig. 8 and table) in all 6 patients, but there was also a definite decrease of power in Cases 5 and 6 with lowering of the potentials during the grip. Clinically, improvement was doubtful, though there was increased well-being in Case 4, who at that time was showing signs of digitalis intoxication. None of the patients showed signs of hypoglycemia.

Glutamic acid reduced spontaneous activity in both patients, and the end point of the myotonia was clearly distinguishable at 1.5 second in Case 2 and 11.5 second in Case 5 (Fig. 9).

Sodium lactate, which was given to 1 patient (Case 2), decreased myotonia within 5 minutes to 3.8 seconds, with almost complete disappearance of the continuous activity (Fig. 10).

DISCUSSION

From the results of our electromyographic studies using surface electrodes, it became apparent that the most prominent feature of the electromyograms was the presence of spontaneous, continuous electrical activity at rest in 4 patients; in 2 patients, we observed the occurrence of the bursts of single high voltage (100 mv.) spikes of variable frequency, usually appearing after a voluntary movement. Slight mechanical stimulation, such as rubbing the skin, tended to increase the amplitude of the oscillations in those patients in whom spontaneous activity was observed. Spontaneous activity was never observed by us in normal persons under the same experimental conditions (Fig. 4).

Buchtal and Clemmensen,[4] using needle electrodes, were the first to observe that, in an apparently relaxed myotonic muscle, there were always small areas of increased electrical activity present, but they did not observe an increase of the electrical activity with the plate electrodes.

Landau[37] reported on the incidence of spontaneous bursts of single oscillations in patients with dystrophia myotonica following a strong voluntary movement, and Floyd, Kent, and Page[8] noted difficulty in obtaining electrical silence in the patients with dystrophia myotonica. The electrical activity of the excitable tissue is dependent on the ionic fluxes across the membrane, and causal relationship has been established between potassium and bioelectrical changes.[14,29] While the action potentials are due to the sudden alteration of the membrane permeability to sodium and potassium ions, it is largely a passive process and is associated with the increased sodium and decreased potassium concentration inside the cell. The reversal of the ionic changes following the action potential requires a supply of the metabolic energy, since ions move against the concentration gradient. During the period of recovery, sodium is extracted and potassium absorbed. The recovery process can be delayed by the metabolic inhibitors or change of temperature.[14,22] The factors that facilitate potassium absorption are glucose,[26] insulin and lacate,[19] glucose and insulin,[32] and glutamic

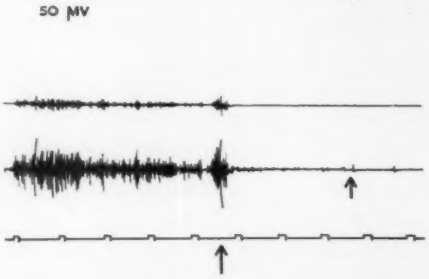

Fig. 8. *(Case 5)* Glucose and insulin test 25 minutes after insulin was given. Relaxation time, 3 seconds

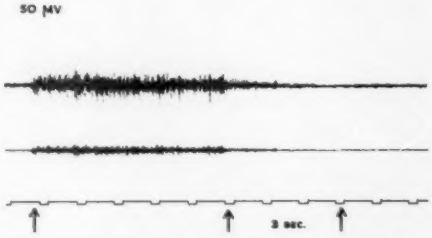

Fig. 9. *(Case 2)* Glutamic acid was given 35 minutes before this recording. Relaxation time, 3 seconds

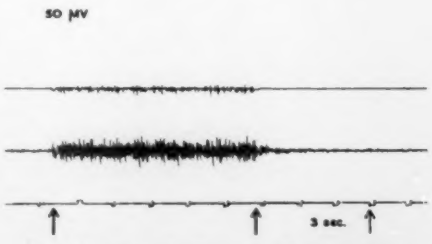

Fig. 10. *(Case 2)* Glucose and M/6 sodium lactate. Recording 5 minutes later shows relaxation time of 3 seconds.

acid,[16] and all are concerned with carbohydrate metabolism.

Studies with the radioactive isotopes of sodium and potassium[2,34] showed a disturbance of the electrolyte level in muscle in cases of dystrophia myotonica, as seen from the decreased muscle potassium and increased sodium, which could account for the increased muscular irritability.

It seems then that the defect lies in the membrane itself, because the stabilizing drugs that have a primary effect on the cell membrane by reducing the leakage of sodium and potassium,[29,33] such as procaine amide and quinine, were most effective in decreasing the spontaneous activity and brought the relaxation time to almost normal time. There was also marked clinical improvement and even an increase of power.

Other groups of drugs were used in an attempt to influence the active transport of the electrolytes to and from the muscle cell and thus decrease muscular irritability. As can be seen from the table and Figure 7, the glucocorticoids were most effective in reducing clinical myotonia, thus further supporting the observations by Martin and Pattee[20] and Liversedge and Newman.[18] In the electromyograms, we could also observe decrease of the relaxation time as well as of the continuous activity. From the experimental work on the rat diaphragm by Flückiger and Verzar,[9] it appears that glucocorticoids cause increased glycogen and potassium deposition in the muscle. That this happens in patients with dystrophia myotonica has yet to be shown.

Gros and Kirnberger[13] reported that glutamic acid improved power in patients with muscular dystrophy. In our 2 patients (Cases 2 and 5) who were given a single dose of glutamic acid, its beneficial effect lasted for approximately one hour, with substantial decrease of the myotonia. Its mode of action[16] was presumed to be on the active transport of the potassium ions into the cells.

Intravenous 1/6 molar sodium lactate in Case 2 relieved myotonia within five minutes. In an unpublished work by North and Saunders,[24] it was observed that the relief of myotonia was almost instantaneous after administration of sodium lactate. Manery,[19] in his work on striated frog muscle, was able to demonstrate increased active uptake of potassium in the muscle in the presence of the insulin and lactate. Ravin[27] has investigated the effect of insulin in the treatment of the dystrophia myotonica. In his experience, the decrease of myotonia was observed 10 to 20 minutes after intravenous administration of 10 units of insulin, when patients were showing signs of hypoglycemia.

In this study, the effects of glucose and 0.1 unit of insulin per kilogram of body weight began to show within 20 minutes and were manifested by a decrease of power, which was accompanied by the lowering of the potentials during the grip. There was also decrease in relaxation time and of spontaneous electrical activity, but clinical improvement was insignificant.

Grob, Liljenstrand, and Jones[12] considered that glucose and insulin were ineffective in causing increased uptake of the potassium in normal subjects, but, in patients with periodic paralysis, there was significant potassium uptake. Grob, Jones, and Liljenstrand,[11] Zierler,[36] Park and associates,[25] Leupin and Verzar,[17] and Calkins, Taylor, and Hastings[5] showed in vitro that glucose and insulin could produce increased glycogen deposition and potassium uptake in the striated muscle.

The increased muscular weakness is hard to account for, but, from the experimental work by Szent-Gyorgyi,[31] it has been shown that a change of potassium concentration of less than 10% might make all the difference between no contraction and maximal contraction. According to McArdle,[21] increase of intramuscular potassium leads to a raised membrane potential. The hyperpolarization would raise the electrical threshold and might result in lowering of the voltage of action potentials.

In conclusion, it might be said that the spontaneous electrical activity observed in the electromyograms in the majority of our patients could be an indication of the increased muscular irritability due to increased permeability of the muscle cell membrane, with a consequent disturbance of the electrolyte equilibrium in the muscle. Furthermore, it has been shown that decrease of myotonia and spontaneous activity could be achieved by administration of those drugs known from experimental work to act on the cell membrane and thus

increase the potassium uptake in the cell. It is not known whether removal of sodium from cells is affected, but some[10,14] consider that the potassium and sodium movements in and out of the cell are coupled. We are aware that there is no proof as yet that these drugs act in the intact human body in the same way as in experiments with isolated tissues. The direct estimation of intramuscular electrolytes before and after administration of the drugs might clear some points.

SUMMARY

1. Clinical and electromyographic investigations were made of 6 patients suffering from the dystrophia myotonica.

2. Electromyograms of 5 patients showed the presence of spontaneous electrical activity, which was manifested as either a continuous activity or bursts of single high voltage spikes of variable frequency. This made the interpretation of the exact end point difficult at times.

3. Effects of the various drugs on the relief of myotonia were assessed by means of electromyography.

4. Possible actions of drugs are discussed in the light of recent experimental work on isolated striated muscle.

The authors wish to express their appreciation to Mr. Ross Speden for helpful criticism and to Mrs. L. Taggart and Mrs. G. Sim for secretarial assistance.

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Reserpine in Huntington's chorea

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EARLY REPORTS by Walther-Büel,[1] Kirkpatrick and Sanders,[2] and Chandler[3] upon the efficacy of reserpine in the control of abnormal movements in Huntington's chorea appeared in 1955. Daily doses of 2 to 5 mg. were employed. A more comprehensive study appeared a few months later, when Lazarte and associates[4] reported their results in 19 patients. Somewhat larger daily oral doses of reserpine, 4 to 11 mg., were administered. Excessive physical inertia or psychomotor retardation was combated by simultaneous administration of amphetamine. The necessary dose of this drug was found not to exceed 10 mg. per day. Motion pictures for comparison of severity of chorea without and with medication were made in 16 cases. Their results were also favorable; they reported no undesirable effects. Since then, similar reports have been published in varying detail.[5–10]

We have treated 10 patients with Huntington's chorea in the manner outlined by Lazarte and associates.[4] In addition to observations upon general behavior, motion pictures were obtained of each patient both before medication and at the time of the optimal drug effect. Single motion picture exposures were standardized at 25 ft. of 16-mm. film. A minimum of 2 such exposures constituted a documentary record for each case, 1 being taken with the patient sitting in a chair and 1 while standing or walking. The latter was possible in all but 1 case. Thus, there was 50 ft. of film for each patient without medication available for comparison with an exposure of equal length while on medication; 1,000 ft. of motion picture film, therefore, constituted the basis for objective comparisons in this study. Doses of reserpine varied from 2 to 10 mg. and of d-amphetamine sulfate from 5 to 45 mg. per day.

RESULTS

Upon comparison of motion pictures made with and without medication, it was apparent that all 10 patients showed a decrease in the severity of chorea with reserpine. These were graded as follows: 2 exhibited moderate (estimated 50%) decrease; in 6, the decrease of chorea was marked (estimated 75%); and in the remaining 2, there was a complete disappearance (100%) of abnormal movements (see table). Undoubted benefit in the well-being of the patients resulted in Cases 2, 3, and 4. Patients 3 and 4 were unable to walk more than a few steps without assistance and experienced frequent falls while attempting to do so before reserpine was given. Both regained the ability to walk unaided while taking the drug. Patient 2 was also unable to walk without assistance. Her chorea was of such severity that she occasionally upset her wheel chair; this degree of violence abated with reserpine, but independent ambulation was not fully restored.

Although chorea was markedly reduced in Cases 1, 5, 6, and 8, it was questionable that a service had been rendered in the alleviation of symptoms. The intellectually deteriorated and emotionally impoverished patient is little incommoded by chorea unless it is sufficiently violent to result in injury or prevent ambulation.

A number of undesirable effects of medication were encountered; 1 patient (Case 5) developed arterial hypotension. This was corrected by ephedrine sulfate, 45 mg., given three times daily. Only 1 patient (Case 6) showed significant evidence of the Parkinson syndrome, which may occur with reserpine therapy; it was not inimical to her motor performance.

Serious untoward effects from reserpine were exhibited by 3 patients and, for various reasons, were not amenable to counteraction

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by other drugs. Of these, 2 (Cases 7 and 9) displayed sufficient loss of interest in self-care and physical and social activities or deterioration of social behavior to vitiate the beneficial effect to the patient of the control of chorea. Patient 7 fell less frequently while taking reserpine, but the adverse effects were great. The other patient (Case 9) was unquestionably better without reserpine. Decrease of chorea in him was attained at a small dose, 2 mg. daily. Doses of amphetamine larger than those indicated in the table were not given to these 2 patients because the drug occasioned anorexia in subjects who were already underweight. The most toxic effect of reserpine was observed in Case 10, profound asthenia having developed with a dose (3 mg. per day) small by comparison with some used. This patient became unable to move his extremities or to raise his head from the bed. Following cessation of reserpine, he regained his former ability in walking and resumed his limited physical activities.

DISCUSSION

Decrease in the severity of the chorea could not be assessed accurately without the aid of motion pictures. There was little agreement among ourselves upon the degree of improvement when our estimates were based upon attempted recollection of the patient's earlier condition. There was little disagreement, however, when we were confronted with the motion pictures. Although all patients showed undoubted decrease in the severity of chorea, other considerations detract from the value of the drug for general use in this disease. Thus, only 3 of our 10 patients were substantially benefited; 4 more, in whom chorea was reduced, could not be considered benefited by this change. This seems comparable to the observation of Walther-Buel[5] that the practical benefit is, at best, a modest one. Further, in our series, there was a significant number of undesirable effects; this has not been emphasized in earlier reports on reserpine in Huntington's chorea. Of our patients, 3 were

Case No.	*Sex*	*Age*	*Duration of chorea*	*Daily dose of reserpine*	*Time to raise dose to optimum*	*Daily dose of amphetamine*	*Estimated decrease of chorea*	*Remarks*
1	M	62 yr.	10 yr.	6 mg.	45 days	30 mg.	moderate (50%)	
2	F	44 yr.	7 yr.	6 mg.	60 days	10 mg.	moderate (50%)	Materially benefited by reduction in violence of chorea while on reserpine
3	M	49 yr.	?	9 mg.	90 days	20 mg.	marked (75%)	Regained ability to walk while on reserpine
4	F	49 yr.	3 yr.	6 mg.	20 days	45 mg.	marked (75%)	Regained ability to walk while on reserpine
5	F	43 yr.	9 yr.	7.5 mg.	60 days	10 mg.	marked (75%)	Hypotension, induced by reserpine, controlled by ephedrine
6	F	63 yr.	8 yr.	6 mg.	30 days	none	complete (100%)	Mild parkinsonism developed with reserpine
7	F	56 yr.	13 yr.	10 mg.	60 days	7.5 mg.	marked (75%)	Excessive deterioration of self-care and loss of drive while on reserpine
8	F	70 yr.	17 yr.	8 mg.	90 days	5 mg.	marked (75%)	Chronic convulsive disorder secondary to Huntington's chorea, controlled by Dilantin
9	M	54 yr.	7 yr.	2 mg.	—	5 mg.	marked (75%)	Excessive deterioration of self-care and of social behavior while on reserpine
10	M	46 yr.	11 yr.	3 mg.	—	10 mg.	complete (100%)	Profound asthenia, amounting to flaccid quadriplegia, while on reserpine

thus seriously affected, 2 by excessive loss of drive and 1 by incapacitating weakness. The daily doses of reserpine in these 3 were 10, 2, and 3 mg., respectively.

All of our patients exhibited some degree of psychomotor retardation; in most, this was partially corrected by amphetamine. It was impressive, however, that the restoration of spontaniety by amphetamine was never complete. Although a patient might walk better while on reserpine, he would walk about only when urged to do so and this motivation was not restored by amphetamine. The mode of action of reserpine upon the chorea is, as yet, unexplained.

The mode of action of reserpine upon the central nervous system has been the topic of a number of studies. Although the work of Bein[11] has been cited[12] as evidence that reserpine exerts some of its effects by direct action upon the hypothalamus, one is impressed on reviewing Bein's work that he stressed the action of reserpine upon systems rather than loci. Studies by Schneider and associates[13] indicate that reserpine counteracts afferent impulses that bring about sympathetic activity rather than having a direct action upon the hypothalamus. Rinaldi and Himwich[14,15] found a stimulating effect of reserpine upon the alerting mechanism of the midbrain and diencephalon of the rabbit. Killam and Killam,[16,17] however, found that the dose of reserpine, 100 μg. per kilogram, which was "clinically effective" for the species, did not alter arousal responses in the cat and point out that the dose employed by Rinaldi and Himwich, 1 mg. per kilogram, was far above this level. Rinaldi and Himwich[14] have also proposed that reserpine cannot be considered a hypnotic drug because it induces an alert electroencephalographic pattern (in rabbit), whereas barbiturates induce a sleep pattern. Loeb, Parma, and Rosadini[18] found, however, that reserpine enhanced physiologic sleep in cats and that the electroencephalographic pattern was consistent. The depressive action of reserpine upon various evoked responses, reported by Gangloff and Monnier,[19] cannot be considered related to its therapeutic action because of the large dose, 1.5 mg. per kilogram, that they employed. It seems that available data do not give a complete picture of the neuronal basis of the action of reserpine upon the central nervous system.

Concepts of the neuronal basis of Huntington's chorea were recently reviewed by Walther-Büel,[5] who pointed out the lack of general agreement on this subject. It appears, therefore, that we are still far from grasping the essence of the action of reserpine in chorea. It is possible, however, to consider the ameliorating effect of this drug upon these abnormal movements from the behavioral point of view, disregarding, for the time being, the ultimate neuronal basis.

It has been common practice to characterize chorea and athetosis (choreoathetosis) as "involuntary" movements.[20–23] A relationship between chorea and "voluntary" motor activity is recognized, however, and this has been discussed in various ways. Brock,[22] for example, describes choreiform movements as being "subjectively purposeful but objectively aimless." Further on, he returns to this relationship with more clarity in defining parakinesis, which, he says, is commonly seen in Huntington's chorea: "By parakinesis is meant a choreiform type of involuntary movement, in which a purposeful voluntary movement is disrupted by bizzare exaggeration, producing a clownish effect." Denny-Brown,[24] of the movements of Huntington's chorea, noted that "in their mildest degree they are difficult to distinguish from simple restlessness or fidgets. The patient does not keep still, the head is moved this way or that, the leg shifts position, the facial expression is disturbed by a grimace. The movements in this slight degree are purposive and, if watched carefully, are seen to repeat in certain patterns which are peculiar to each patient." Later, however, he says: "All these movements are purposeless and are related to voluntary movement only in that they are superimposed upon it." Our observations have led us to close attention to this blending of "voluntary" movement with chorea and have left us with less confidence in their separability than has often been implied. Neither physiologist nor psychologist has, thus far, provided us with means whereby we may objectively distinguish between "voluntary" and "involuntary." The dichotomy is based upon intuitive appraisal by the physician and subjective interpretation by the patient.

In the opportunity afforded by the motion pictures to repeatedly view the same movements, we were struck by the difficulty, if not impossibility, of designating a given movement "voluntary" and another "involuntary." Consequently, our position now is this: In Huntington's chorea, one sees a continuous flow of distorted movements, to which the concepts of voluntary and involuntary are, at best, poorly applicable. Fully developed chorea affects the individuals every waking moment; none of his spontaneous movements are free of it. He can express himself in motor behavior (psychomotor activity) only in this distorted manner. It is to psychomotor activity, or, as Freyhan[25] has so well named it, "psychomotility," that we wish to turn attention in this disease.

It is characteristic of Huntington's chorea that the abnormal movements bear a resemblance to normal "psychomotility." This is clearly evident in Denny-Brown's[24] description quoted above; no term more suitable than "fidgets" could have been chosen to express this relationship. Fidgets are only restless movements in one person but early chorea in another. The observation that the movements repeat in patterns peculiar to each individual suggests a psychomotor element in their origin. If we can free ourselves from the traditional, intuitive assumption that chorea is necessarily "involuntary," we shall have a new point of departure for understanding chorea and the action of reserpine upon it. It has already been noted that psychomotor drive is reduced by reserpine in this disease, as well as in other applications of the drug. Although amphetamine opposes this action, this opposition is incomplete. Freyhan[25] has concluded that, in psychiatric disorders, reserpine (and chlorpromazine) is most effective in those conditions that exhibit hypermotility and increased initiative and affective tension. He also points out that the gradual reduction of psychokinetic activity produced by the drug cannot be broken down into "normal" versus "extra pyramidal" motility patterns.

Superficially, it appears that, in Huntington's chorea, reserpine suppresses 2 aspects of motor behavior: abnormal "involuntary" movements and psychomotor activity. Our conclusions for the action of the drug in this structural disease are harmonious with those of Freyhan[25] for the psychiatric disorders. In both instances, one feature of the disorder is hypermotility; this is decreased by reserpine. We conclude that the drug does not suppress 2 separable aspects of behavior but that chorea is dependent upon, if not identical with, "psychomotility." If they are identical, then chorea (Huntington's) is simply an abnormal form of psychomotility, seen when the central nervous system has been altered in a specific way.

SUMMARY

Treatment with reserpine and amphetamine was given to 10 patients with Huntington's chorea. The severity of chorea was reduced in all, but only 3 patients were considered benefited; 3 more suffered serious undesirable effects with doses required to suppress chorea. Reserpine is of value in Huntington's chorea only when the movements are dangerously violent or when they prevent independent ambulation. The neuropharmacology of reserpine and the physiologic basis of chorea are both incompletely understood. Attention is called to the imperceptible blending of chorea and "voluntary" motor activity in this disease and to the absence of objective criteria for distinguishing between voluntary and involuntary movements. Because of the apparent simultaneous decrease of chorea and psychomotility and because of our inability to distinguish between them, it is suggested that chorea (Huntington's) is a distorted form of psychomotility. This concept of chorea is offered as an alternative to the assumption that, in individuals with this disease, all motor activity can be separated into 2 distinct categories, voluntary and involuntary.

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Ischemic neuropathy in necrotizing arteritis

G. W. Holt, M.D.

PERIPHERAL NEURITIS may be an initial sign of the arteritis of collagen diseases: periarteritis nodosa,[1] lupus erythematosus, scleroderma, dermatomyositis, and rheumatoid arthritis. In these, the neural lesion is the result of arteritis of the vasa nervorum.[2,3] Central nervous system involvement is secondary to vasculitis of its small arteries and arterioles. Nervous system changes are ischemic in origin.

In the natural course of one collagen disease, rheumatoid arthritis, necrotizing arteritis with ischemic neuropathy rarely occurs. The complication of arteritis has been reported with increasing frequency since the introduction of corticosteroids in the suppressive treatment of rheumatoid arthritis. In the past five years, 36 cases of steroid-treated rheumatoid arthritis have been reported as showing arteritis at necropsy by Kemper, Baggenstoss, and Slocum,[4] Sokoloff and Bunim,[5] Irby, Adams, and Tonne,[6] Johnson and associates,[3] and others. In these 36 cases, necropsy revealed necrotizing arteritis resembling or indistinguishable from periarteritis nodosa. In each case, the arteritis was considered to have been partially or wholly responsible for the fatality. Involvement of the nervous system was common.

Since a previous report[3] of 3 necropsy cases, a patient has been observed whose clinical syndrome resembled that of the fatal cases but who survived following withdrawal of corticosteroid treatment. In this patient, the vasculitis was manifested by peripheral neuritis, a mal perforant of the sole, and gangrene in punctate form only. A comparison of the data in fatal and nonfatal cases is of neurologic interest. This comparison indicates that therapeutic arteritis varies in severity. Alteration of the therapeutic regimen may reduce the mortality rate of arteritis associated with prolonged intensive steroid treatment of rheumatoid arthritis. The patient who has severe symptoms of arteritis and neuropathy may recover.

In the fatal cases with demonstrable arteritis at necropsy, the clinical picture suggested that the triad of progressive neuropathy, multiple organ involvement, and constitutional responses could be characteristic. Of this triad, neuritis was the first to become apparent. It is therefore of importance to understand the neural lesion, since it may indicate the disease in process prior to full clinical development. The neuropathy was insidious in onset. The patient complained occasionally of pain, paresthesia, and mild numbness. The neuropathy began peripherally, first in the foot and then in the hand. Examination demonstrated foot drop and wrist drop. At first intermittent, the foot and wrist drops became permanent and were followed by progressive ascending motor involvement. Sensory deficit occurred later. The sequence of pain and paresthesia, then ascending paralysis, and later sensory deficit suggested an ischemic neuropathy. Since the arteritis is disseminate, the description of the paralysis as ascending is more apparent than real.

In the second phase of the triad of this disease, there was multiple organ involvement. Alternate advancement and improvement in vasculitis symptoms occurred. Concurrent cardiac, cerebral, pulmonary, renal, and intestinal symptoms added to the complexity of clinical findings as the neuropathy advanced. This disseminate character of the visceral involvement

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Fig. 1. Cyanosis (impending gangrene) of digits

created a capricious quality in clinical symptoms from one day to the next. Glaser[2] has pointed out that neural symptoms and signs in collagen disorders may be affected by secondary disturbances, such as azotemia, fever, hypertension, congestive failure, hemorrhagic tendencies, or the toxic effects of treatment.

Thirdly, constitutional and laboratory responses were characteristic of progressive arteritis. These reactions included fever, chills, anemia, weight loss, sweating, tachycardia, leukocytosis with shift to the left, and increased erythrocyte sedimentation. In 1 of 3 fatal cases, positive L.E. cell preparations were demonstrated. Some of these responses are a caricature of sepsis; however, cultures of blood, urine, and necropsy specimens in the patient with fatal arteritis were sterile. In the absence of infection, septic-like constitutional responses are often indicative of arteriolar insufficiency with resultant ischemia, anoxia, and necrosis. Indeed, in sepsis, the occurrence of fever, chills, tachycardia, and sweating poses a question regarding an alteration of arteriolar functions. The extent to which such responses and alterations are related to reactive, reparative, immune, or protective mechanisms is undefined and probably worthy of further investigation.

The clinical picture is a reflection of the segmental and focal character of the vessel lesion. The affection is predominately of small arteries and arterioles rather than large arteries. There is simultaneous occurrence of healing and advancement in different areas in the same vascular region. Relative susceptibility of neural tissue to ischemia may account for neuritic symptoms occurring early in the syndrome. Permanent neural damage preceded gangrene, suggesting that nerve tissue is more susceptible than skin to ischemia.

The recognition of this triad of progressive predominately motor neuropathy, multiple organ disease, and constitutional responses may facilitate the diagnosis of arteritis as is shown in the following case.

Case 1. A 51-year-old, postmenopausal, white housewife was in normal health until she was 47 years of age. Then, progressive deforming rheumatoid polyarthritis developed. Thereafter, cortisone was administered daily in doses of 25 to 75 mg. Supplementary treatment with other corticosteroids, corticotropin, gold, and salicylates was given occasionally. Hypercortisonism was apparent early in 1956.

In November 1956, three and a half years after the first arthritic symptom, burning, tingling, and paresthesia of the hands and feet developed. There were shooting pains along the peripheral nerves. Foot drop and later wrist drop appeared. At first, these ischemic symptoms were intermittent. Established signs and symptoms temporarily improved. The paralysis slowly ascended. Subjective and later objective numbness occurred. Pain diminished as hypalgesia and paralysis spread proximally in the extremities. Six months after the first neuritic symptoms, there was generalized paralysis and areflexia. Objective numbness had advanced proximally to knee and elbow. Vibratory perception and position sense eventually disappeared in the lower extremities. Severe sensory loss developed as multiple systems became involved. This may suggest that such signs are, in part, a result of visceral disease.

Signs and symptoms of multiple system disease became perplexing. Pleural pain and angina were difficult to interpret. Abdominal crises with intestinal hemorrhage occurred twice. Tachycardia was common. The personality facade of varying lethargy and alertness, distractibility, emotional instability, and affective inappropriateness identified cerebral involvement. Purpuric or hemorrhagic skin lesions suggested cutaneous capillary vasculitis. Urine specimens frequently contained as many as 100 erythrocytes in each high power field. Punctate areas of gangrene, black in color, appeared, first on the summit of the rheumatoid nodules and then in the nail cuticle. Violaceous cyanosis ascended gradually in the digits and distal portions of the hands and feet (Fig. 1). This cyanosis differed from Raynaud's phenomenon by its asymmetric digital distribution, its unresponsiveness to cold or heat, and its continuous presence

distal to a circumscribed line. Punctate gangrenous areas in the cuticle were replaced by frank necrosis at the base of the nail (Fig. 2). Dry gangrene was most prominent in the finger tips and around the wrists and ankles. Viable tissue between the gangrenous areas of the terminal phalanges and the wrist and ankles suggested a disseminate arteritis of small arteries in the periphery of the extremity with normal large arterial trunks proximally (Fig. 3).

Constitutional symptoms became prominent in the two months prior to death. A chill and high fever occurred daily. The leukocyte count was as high as 38,000 per cubic millimeter. The erythrocyte sedimentation rate was elevated to 40 mm. per hour (Westergren). Although these constitutional symptoms and signs initially suggested sepsis, cultures of the urine, blood, and biopsy specimens were sterile. On 2 occasions, L.E. cells were demonstrated; 3 biopsies in different areas six weeks before death failed to reveal any arteriolar abnormality. In June 1957, an acute coronary thrombosis developed. Two weeks later, she died in respiratory failure.

Necropsy revealed disseminate necrotizing arteritis indistinguishable from periarteritis nodosa. In the viscera, small arteries and arterioles had thickened, nodular walls and pin-hole lumina. Microscopic examination disclosed a segmental arteriolitis with cellular proliferation, inflammation and necrosis of the vessel walls, reduplication of elastic laminae, and intimal proliferative occlusion. Necrotizing arteriolitis was severe in the vasa nervorum of the vagus nerves (Fig. 4).

Fig. 2. Gangrene of the terminal phalanges

Case 2. A 39-year-old housewife was admitted in December 1957 for mal perforant necrosis of the left foot. She had been treated intensively with corticosteroids over a period of five years for progressive rheumatoid polyarthritis. Deep x-ray therapy for pelvic pain presumed to be the result of endometriosis was being given at the time of admission. Hypercortisonism was present.

Neurologic examination revealed motor weakness of the digits, loss of Achilles reflexes, hypalgesia distal to midfoot and midhand, analgesia of the mal perforant extending into the intermetatarsal area, asymmetric cyanosis (impending necrosis) of hands, feet, and digits, and punctate gangrene in the nail cuticle and in the centers of the summits of rheumatoid nodules. Pericardial friction rub and precordial pain were observed. Abdominal crisis and intestinal bleeding occurred on one occasion. The liver edge was palpable 5 cm. below the costal margin. Fever did not exceed 101° F. Leukopenia and anemia were present. The erythrocyte sedimentation rate varied between 40 and 100 mm. per hour.

Cortisone was withdrawn over a three-week period. Corticotropin (ACTH) was given during this time, and then all hormones were discontinued. Adrenal insufficiency was not a serious problem. Within one week after discontinuation of the hormones, all punctate areas of gangrene were replaced with a white scar. Cyanosis gradually cleared. The necrosis of the sole healed. In addition, all rheumatoid nodules disappeared. Hypertension receded. Peripheral neuritis gradually improved. For over one year, this patient has remained free of symptoms of arteritis. The arteritis is presumably either in remission or has resolved.

Fig. 3. Viable tissue between gangrenous areas in the finger tips and wrists. This would indicate arteritis of small vessels. The radial pulses were palpable.

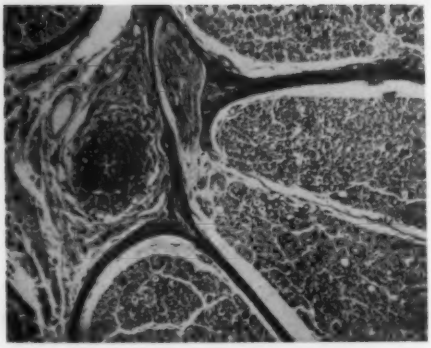

Fig. 4. Cross section of nutrient arteriole of vagus nerve sectioned at the level of the superior mediastinum. Changes in the lumen and wall of the arteriole are consistent with necrotizing or periarteritis nodosa. Demyelination of the nerve is probably consistent with ischemic neuropathy.

The essential difference in these 2 cases is one of severity. In the fatal case, there was progression of a motor neuropathy, fever above 101° F., evidence of multiple system disease, severe constitutional signs, and gangrene. Administration of cortisone continued until death. In the patient who survived, the neuropathy was limited, fever did not exceed 101° F., multiple organ disease and constitutional signs were mild, and gangrene occurred in punctate form only. In this patient, cortisone withdrawal was completed within three weeks after admission to the hospital.

DISCUSSION

Vasculitis: susceptibility and sensitizing therapeutic agents

These observations suggest that cortisone is related to the development of periarteritis nodosa and secondary neuropathy in steroid-treated rheumatoid arthritis patients. The mechanisms involved in the development of the vasculitis are not a simple cause-effect relationship. This is shown by the observation that only a small number of steroid-treated rheumatoid arthritis patients develop arteritis. This reaction to a therapeutic agent may be reviewed in reference to what is known about the development and prevention of such reactions. In the pathogenesis of arteritis in steroid-treated rheumatoid arthritis, the significance of various vascular changes in drug reactions is of importance, as is the relation of vascular reactions to neural disorders in general.

Arteritis of the necrotizing type has been documented in "untreated" rheumatoid arthritis, periarteritis nodosa, lupus erythematosus, scleroderma, and dermatomyositis before the steroid era. Increased spontaneous occurrence or diagnostic awareness cannot account for the greater frequency of necrotizing arteritis in corticosteroid-treated rheumatoid arthritis patients. The increase in incidence must be assumed to be a result of an adverse reaction between a therapeutic agent and a state of potential susceptibility present in only a few rheumatoid arthritis patients.

Factors in susceptibility. Individual variation in susceptibility is not understood. The author believes that susceptibility is infrequent and that the vascular system is primarily susceptible. In this respect, in these patients the arthritic joints were not modified by the development of periarteritis nodosa. Changes in other systems can be accounted for as an ischemia secondary to arteritis. It has been postulated often that previous infectious processes or abnormal immune responses may increase susceptibility and predispose to arteritis. Allergy has been frequently related to susceptibility. Vasculitis complicating steroid-treated rheumatoid arthritis often occurs in the hypercortisoned patient and in the climacteric period of life, thus implying that prolonged treatment and an endocrine or age factor may be partly responsible.[3]

Therapeutic agents and hypersensitization. Different authorities have believed that hypersensitization to drugs may be related to periarteritis nodosa. Such therapeutic agents include penicillin, cortisone, sulfonamides, arsenicals, vaccines, antigens, and allergens. The relation between these drugs and periarteritis nodosa is difficult to define. Therapeutic agents may have been employed when a disease process, often unidentified, was present in the host. Cause and effect are not easily evaluated when periarteritis nodosa follows a disease treated with one or more drugs. It would appear that the arteriole and small blood vessels participate in hypersensitization. Reactive, pro-

tective, and immune responses to the disease or the therapeutic agent or both may contribute to hypersensitization.

Vascular responses to hypersensitization. The role of arterioles and small blood vessels in the natural course of disease and in therapeutic response has been of interest since the beginning of this century. Herxheimer[7] in 1902 described, clinically and pathologically, the engorgement and infiltration incited in maculopapular syphilids by the initial mercurial inunction. The syphilid change is a therapeutic vascular reaction. In the half century since the original description, this phenomenon has been shown to occur also as a generalized reaction. It is now recognized that the Herxheimer phenomenon, in part, has an immunotherapeutic basis. Herxheimer[8] in his late publications stated that the reaction was not always specific for syphilis and was probably similar to the tuberculin reaction. More recently, Sheldon and Heyman[9] have stated, "The morphologic changes occurring in syphilitic lesions during the Herxheimer reaction are essentially those found in the tuberculin reaction, but are less severe and both are non-specific." They pointed out that the histologic changes encountered in syphilitic lesions during the clinical Herxheimer reaction involve chiefly the small blood vessels. They also stated, "It is significant that these morphologic changes do not occur in the natural course of syphilitic infection, but are observed only following treatment." One may assume that signs of the Herxheimer reaction, such as hemorrhage, purpura, thrombosis, necrosis, joint effusion, and perivascular changes, are likewise related to the functional and morphologic small vessel changes. These changes are a direct result of treatment. Catastrophic Herxheimer reaction has been referred to as therapeutic shock. Therapeutic shock may affect one or many viscera, may be immediate or delayed, and may be fatal in any case.

A second therapeutic vascular reaction, not limited to small vessels, may occur in luetic arteritis, tuberculous arteritis, or periarteritis nodosa. This reaction, known as therapeutic paradox, consists of "complete healing" with occlusion of an arteritic lesion. In the healing process, luminal occlusion with secondary visceral ischemic necrosis occurs. The therapeutic paradox may prove fatal; 2 well documented arteriolar reactions—therapeutic shock and therapeutic paradox—propose certain common denominators in the interpretation of other types of therapeutic vascular changes. The author believes that vascular hypersensitization is related to both therapeutic shock and therapeutic paradox.

Pathogenesis of hypersensitization. It has been commonly accepted that one reaction to foreign protein is a hypersensitization in which the arterioles and small vessels undergo functional and morphologic changes. An effect of these changes is ischemia. Bacterial infection, the common source of foreign protein, may therefore produce a reactive ischemia. Immunologists agree that hypersensitization may cause necrosis. Hypersensitization has been interpreted as an antigen-antibody reaction between foreign protein and the small blood vessels. Landsteiner and van der Scheer[10] have shown that a chemical, ordinarily nonantigenic, when combined with protein may become capable of producing sensitizing antibody. On this basis, Rich[11] postulated that certain chemotherapeutic agents, when bound by plasma protein, form a drug-protein complex that may produce sensitizing antibody. Chemotherapeutic agents bound by plasma protein act as foreign protein in producing hypersensitization. Rich also stated that sulfonamides and iodides bound by plasma protein could produce prolonged anaphylactic hypersensitivity, thereby resulting in periarteritis nodosa.

Rose and Spencer[12] agreed that antithyroid drugs may cause periarteritis nodosa but postulated abnormal immune response to bacterial infection as the cause in most cases. Zeek, Smith, and Weeter,[13] on the basis of causation and morphology, classified such vascular reactions as hypersensitivity angiitis and periarteritis nodosa. French[14] reported 76 fatal cases in which sulfonamides were considered to have caused sensitization. The vessel changes consisted of fibrinoid necrosis, endothelial edema, proliferation, endarteritis, and periarteritis. More, McMillan, and Duff[15] referred to the arterial lesion in sulfonamide sensitization as polyvasculitis rather than periarteritis nodosa. In 7 cases, they regarded the polyvasculitis as having caused death.

These observations suggest that corticosteroids may combine with plasma proteins. If plasma proteins, when combined with corticosteroids act as a foreign protein, prolonged hypersensitization and periarteritis nodosa is a possible end result in susceptible long-term corticosteroid-treated rheumatoid arthritis patients.

Effects of hypersensitization: arteritis and ischemia of the nervous system

In necrotizing arteritis, a thickened vascular wall and pin-hole or thrombosed lumen in the vessels of the nervous system produce one salient condition—ischemia of the tissues. The physiologic counterparts of the morphologic changes in the vessels are alterations of flow, pressure, and permeability. The vasculitis and ischemia are disseminate in the nervous system. Ischemia in the nervous system resulting from periarteritis nodosa associated with steroid-treated rheumatoid arthritis is characterized by mild sensory symptoms, then ascending paralysis, and, finally, sensory deficit. The disseminate distribution of the arteritis would suggest that the clinical findings should conform to no other pathoanatomic description. However, observations that motor symptoms are more severe than sensory deficit, that paralysis ascends from the periphery, and that ischemia and attendant anoxia are clinically manifest first in the periphery of the extremity suggest the following conclusions. Pain and paresthesia warn of beginning sensory fiber ischemia. Because the demand for blood and oxygen for neuromuscular activity exceeds that for sensory perception, the motor system appears to fail first. Therefore, paralysis precedes sensory deficit. Common observations in atherosclerotic peripheral vascular insufficiency confirm the fact that weakness exceeds sensory deficit during claudication. The possibility of vasculitis and ischemia as etiologic factors should be considered early in ascending lesions with predominate motor deficit.

Ischemia in other neuropathies. The etiologic factors in the neuropathies associated with immunization are unknown. Hypersensitization has been considered to be one explanation. Other concepts have been advanced, but much remains to be learned regarding pathogenesis of the neuropathy. The significance of microscopic vascular and perivascular changes have not been clarified. Van Rooyen and Rhodes[16] have suggested that polyneuropathy following immunization for rabies, typhoid, tetanus, pertussis, and other diseases is, in part, a result of intravascular thrombosis. They also postulated an antigen-antibody hypersensitization reaction. In this reaction, they believed that, in some instances, the brain tissue of the vaccine was an antigen and that the vascular walls and perivascular tissues were the shock organs of the antibody. If this is true, ischemia may be one factor in the development of the signs and symptoms of the immunization polyneuropathies.

The author believes that postinfection polyneuropathy following diphtheria may be a hypersensitization reaction involving the vessels and cells of the nervous system. The differentiation of postdiphtheritic polyneuropathy from Guillain-Barré's syndrome is not possible unless antecedent diphtheria is proven. Albuminocytologic dissociation is common to both diseases. The etiology of many cases of Guillain-Barré's disease remains obscure. In the majority of cases, there is a preceding symptom complex suggestive of infection, usually involving the respiratory or gastro intestinal tracts. In Guillain-Barré's disease, Baker[17] reported as follows: "In the more acute cases, there occur only vascular changes with distention of the perivascular spaces, while in the more prolonged cases, there often result perivascular myelin destruction and extensive cell alterations." Gilpin, Moersch, and Kernohan[18] observed thickening of the vessel wall and narrowing of the lumen of the vasa nervorum of peripheral nerves in 2 cases of Guillain-Barré polyneuritis. In 1 case, the walls of the vessels were lumpy and contained amyloid.

Landry's paralysis, predominately an ascending motor lesion, could not be distinguished from acute febrile polyneuritis by Osler.[19] Haymaker and Kernohan[20] proposed that Landry's paralysis and the Guillain-Barré syndrome be given the eponymic name of Landry-Guillain-Barré syndrome. After reviewing the literature of both syndromes and conducting a clinicopathologic study of 50 fatal cases, it was their impression that all cases fell into the same category. Their pathologic observations included "scattered petechiae in

the grey matter, especially that of the spinal cord in about one-third of cases" and "a common finding of engorgement of vessels of the leptomeninges and roots of the spinal cord." Lesions were concentrated in the spinal division of the peripheral nerves. Haymaker and Kernohan stated, "No conclusive evidence regarding the etiology of the disorder is presented, although the association of infectious mononucleosis has been proved in two cases and suggested in six of our cases." Although no conclusion can be reached in regard to the etiology of Landry-Guillain-Barré syndrome, speculative interest may attach to the possibility that infection, then hypersensitization, and later vascular dysfunction play a part.

Vasospasm has been postulated as the cause of the ischemic changes in the peripheral and central nervous system in porphyria by Denny-Brown and Sciarra.[21] These authors demonstrated "nerve cell changes in two cases of porphyria which were identical with those found in the dorsal root ganglia in 'Landry's paralysis' by Sweiger (1909) and Bauer (1909)." They also stated, "It is clear that many cases of ascending motor paralysis are in reality porphyric 'neuritis' as was pointed out by Grunewald (1922)." Denny-Brown and Sciarra identified the pathologic process in peripheral nerve and central white matter in porphyria with what they had described previously as resulting from experimental prolonged ischemia. Their pathologic observations did not reveal any morphologic changes in the blood vessels of the nervous system in porphyria. They concluded that there was an impairment of myelin compatible with patchy and intermittent ischemia mediated by vasospasm. Schwarz and Moulton[22] found in a fatal case of porphyria edematous, exudative, and proliferative vascular changes. They concluded, "There seemed to be little evidence in this study to relate the vascular with the neuronal changes, although here and there this was suggested." Hierons,[23] after observing 5 cases of acute porphyria, concluded, "The peripheral nerve lesions probably result from a metabolic disturbance and not from vasospasm while extensive vascular lesions can occur in the brain, but these are probably secondary to severe hypertension or respiratory paralysis."

Ischemia in the nervous system in periarteritis nodosa. Lovshin and Kernohan[24] and others have commented on the ischemic character of the peripheral nerve changes in periarteritis nodosa. In necrotizing arteritis neuropathy occurring in corticosteroid-treated rheumatoid arthritis, the arteriolar alterations in peripheral nerves cannot be differentiated from those of periarteritis nodosa. More and Movat[25] found that the classical necrotizing arterial lesions in 2 cases of polyarteritis nodosa were always associated with a plasma cell reaction. This they regarded as morphologic evidence for the hypersensitive pathogenesis of the necrotizing arterial lesions. Ehrich[26] postulated that "the common denominator of the various collagen diseases lies in their pathogenesis, or, more precisely, in the production by these of abnormal globulins, apparently by plasma cells causing injury of the general mesencyme."

CONCLUSIONS

Any alteration in the small vessels of the nervous system may be of significance. Vascular changes occurring in the arteritis of steroid-treated rheumatoid arthritis patients may be productive of altered intravascular pressure, reduced rate and volume of flow, and diminished permeability. Ischemia and oxygen deprivation of nerve tissue are natural consequences. Kubicek, Holt, and Kottke[27] have pointed out that nerve cell damage may be significant at an oxygen saturation level at which cyanosis begins (80%). At this saturation, the partial pressure of oxygen has decreased from 100 to 45 mm. Hg (Barcroft). This decrease in partial pressure of oxygen represents a considerable drop in the force delivering oxygen from plasma to cell. Vascular and perivascular infiltration and cellular debris increase the resistance to diffusion of oxygen from plasma to nerve cell. Cyanosis suggestive of impending gangrene in the periphery of the extremities of patients with arteritis would indicate that ischemia is of such magnitude as to seriously impair the function of neural tissue as well as skin.

Hypersensitization may lead to focal ischemia of tissue of the nervous system. This mechanism may be one of several contributing to the polyneuropathies associated with immunization, diphtheritic and other postinfec-

tion states, drug sensitization, the Landy-Guillain-Barré syndrome, and the arteritis of steroid-treated rheumatoid arthritis. Respiratory paralysis and generalized anoxia in these diseases also may be productive of functional and morphologic vascular changes.

SUMMARY

The syndrome of neuropathy, multiple system disease, and constitutional responses is suggestive of fatal necrotizing arteritis when occurring in corticosteroid-treated rheumatoid arthritis patients. In patients with limited peripheral neuritis who have only cyanosis and punctate gangrene, remission may occur after cortisone is withdrawn. The sequence of development in progressive neuropathy is as follows: The sensory symptoms of pain and paresthesia occur initially. Paralysis, first in the periphery of the lower extremity, ascends and constitutes the major portion of the neuropathy. Sensory deficit appears after paralysis is widespread. Multiple system disease and constitutional signs develop as the arteritis disseminates in the viscera. Secondary ischemia of the tissues of the viscera, including the nervous system, results from the arteriolar changes.

In the natural course of many diseases, as well as during their treatment, the arterioles and small vessels are affected. Mechanisms that produce the vascular changes include bacteriotoxin reactions, antigen-antibody reactions, abnormal immune responses, therapeutic chemical sensitizations, and others. These mechanisms result in hypersensitive reactions of the vascular system and other tissues.

Hypersensitive arteritis occurs as a result of foreign protein reactions. Similar sensitization and arteritis are believed to be a direct result of the binding by plasma proteins of therapeutic agents. The early symptoms and signs of hypersensitive arteritis are often those of ischemic neuropathy. The development of ischemic changes in the nervous system during the chemotherapy of disease suggests the presence of therapeutic arteritis. This arteritis may be considered more or less related to the Herxheimer reaction, the tuberculin reaction, therapeutic shock, and therapeutic paradox as therapeutic phenomena.

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Symptoms and diagnosis of diastematomyelia

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DIASTEMATOMYELIA represents a congenital malformation in which the spinal cord is divided longitudinally into 2 portions by a bony, cartilaginous, or fibrous septum arising from the anterior aspect of the spinal canal. It is usually seen in childhood but also has been reported in adults.[1–4] Although this condition has been recognized more frequently in recent years,[5–8] the significance of its clinical aspect needs to be emphasized. Early diagnosis and treatment are of utmost importance.

The septum divides the neural canal partially or completely for a distance of one or several segments in the anteroposterior axis and transfixes the spinal cord. The cord is thus immobilized at a certain level and is not permitted to ascend in the neural canal with the longitudinal growth of the vertebral column. With growth, traction is exerted on the fixed spinal cord, and progressive neurologic deficit involving especially the lower extremities is likely to ensue. This anomaly is most common in the lower thoracic and upper lumbar regions but has been seen in the upper dorsal and the lower lumbar areas. It may be associated with other skeletal, cutaneous, and central nervous system anomalies, such as spina bifida, myelomeningocele, lipoma, and dermoid or arachnoidal cysts. In a few instances, the septum has been reported to protrude between the nerves of the cauda equina and not involve the spinal cord;[3,4] it produced clinical signs of nerve root irritation similar to those associated with a protruded intervertebral disk.

The majority of the patients reported in the literature showed congenital cutaneous defects over the spine, congenital deformities of one or both lower extremities, and neurologic disorders.[9,10] The association of congenital defects, neurologic disorders, and roentgenologic evidence of anomalies of the spinal column (spina bifida occulta) should raise suspicion of the presence of diastematomyelia and clearly requires further investigation.

This report is based on the observation of 8 verified cases of diastematomyelia. The diagnosis was made preoperatively in 6 cases; in 2 cases of myelomeningocele, diastematomyelia was not suspected but was discovered at the time of repair in one and at autopsy in the other.

INITIAL SYMPTOMS

The presenting symptoms of most patients with diastematomyelia are referable to the lower extremities or the back. The most common disturbance is difficulty in walking or in learning to walk, associated with deformities involving one or both feet, the toes, or the entire lower extremity. Even though the foot deformity may have been present since birth, only when the child starts to stand or walk do the parents become aware of impairment, prompting them to seek medical help. In some instances, the symptoms leading to medical investigation are those produced by ulceration and complicating infection of the toes.

Low back pain associated with radiating pain in the lower extremities is another frequent initial symptom, which, in children, is difficult to evaluate. Only when the parents notice that the child holds its back straight and stiff, does not stoop, refrains from playing, and prefers to remain quiet or even stay in bed do they become impressed by the child's complaints of back pain. Occasionally, persistence of urinary and, more rarely, fecal in-

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continence is a further reason for seeking medical advice.

Babies born with myelomeningoceles are referred for treatment soon after birth. In these, however, diastematomyelia is not the obvious anomaly and usually is an incidental finding either at the time of the repair of the myelomeningocele or at autopsy.

CLINICAL EXAMINATION

Examination of these patients usually reveals defects involving the skin, skeletal anomalies, and neurologic disturbances.

Cutaneous defects are present in most patients. Except in the cases of myelomeningocele, there is a localized area of hypertrichosis characterized by a profuse growth of long, soft, silky hair lying in the midline of the back, usually over the region of the underlying bony anomaly but not necessarily over the area of the diastematomyelia itself. This abnormal hair growth is present at birth and may be associated with other less obvious skin defects, usually over the spine but not necessarily in the area of hypertrichosis. Inspection may also show discrete dimples, dermal sinuses, bulging subcutaneous fatty tumors, and abnormal bony protrusions. Pigmented nevi or hemangiomas also have been reported.[4,9,10]

Although spina bifida occulta occurs in all cases, it cannot always be detected by clinical examination. However, when noticeable, it is of diagnostic value.

Abnormality of the lower extremity is usually apparent soon after birth but is not constant in type. Unilateral or bilateral equinus deformity, calcaneovarus deformity, shortening of a foot or leg, and hammer deformity of the toes are all easily detected. Except for obvious subcutaneous bony protrusions, associated vertebral deformities are usually not prominent in early age. However, as the child grows older, vertebral deformities become more apparent and produce lordosis, kyphosis, or scoliosis with associated abnormal posture and deformities of the abdomen and thorax. Occasional rib deformities are not easily detectable clinically.

Neurologic disturbances are usually present but variable in association with deformity of the lower extremity. They are characterized by impaired function of one or both lower extremities, weakness and paresis of the flexors or extensors of the foot and toes unilaterally or bilaterally, atrophy of various groups of muscles, absent or diminished patellar or Achilles reflexes, and the occasional presence of Babinski signs. Segmental areas of sensory disturbances may be present but are difficult to evaluate in the infant or young child and, therefore, are not always reliable. However, in children old enough to wear shoes, ulceration and infection may develop on an analgesic area of the foot. Rectal and vesical sphincteric impairments are less common than motor or sensory disturbances of the lower extremities and become more evident as the child grows older. Disturbance in bladder function may lead to inadequate drainage, hydroureter, and hydronephrosis and later result in severe disturbance of renal function. Impairment of function of the rectal sphincters may lead to fecal impactions and dilation of the large intestine. In the presence of myelomeningocele, loss of motor function and of sensations and reflexes below the level of the lesion and incontinence are obvious.

Neurologic disturbances may not be present or be very discreet in patients whose initial symptoms are back or leg pain and who have no obvious deformity of the lower extremity.

Spinal fluid studies do not offer much help in making a diagnosis. Usually, circulation of spinal fluid is not obstructed; manometric findings, the total protein, and cell count are rarely abnormal.

ROENTGENOLOGIC DIAGNOSIS

Orthopedic disorders of the lower extremities, disturbances of bladder and rectal function, trophic skin disorders of the lower extremities, or chronic back and leg pain in children require thorough roentgenologic examination. Whether or not neurologic disturbances are present, skin defects, hypertrichosis, and foot deformity should prompt a search for an underlying vertebral anomaly. Spina bifida with a fusiform widening of the spinal canal occurs in all cases of diastematomyelia. Produced by an increase of the interpedicular distances but no erosion of the pedicles, this widening of the canal extends over several segments and is usually greatest at the level of diastematomyelia. It is often associated with

partial or complete fusion of the involved vertebral bodies, fusion of adjacent laminae or spinous processes, narrowing or absence of intervertebral disk spaces, and, less commonly, hemivertebrae. The characteristic bony spicule producing a line of increased density in the center of the widened spinal canal and reported by many investigators[11,12] is not necessarily present; such a shadow will not be seen if the cord-dividing septum is cartilaginous or fibrous in nature and may not be related to the age of the patient. The bony spur may, at times, be eccentric and fused or attached by fibrous tissue to one of the rudimentary laminae of the open neural arch.

Definite confirmation and accurate localization of the level of diastematomyelia can best be obtained by myelography. In this procedure, the anomaly is demonstrated by a splitting of the opaque column of dye into 2 columns passing around the fusiform defect produced by the bony, cartilaginous, or fibrous septum. The split in the dye column is usually longer and wider than the visualized bony spur. Myelographic studies also may reveal associated congenital tumors, such as lipoma, dermoid, or arachnoidal cysts. Such lesions may produce a complete block of the column of dye above or below the diastematomyelic defect.

Myelographic examination is essential not only in the diagnosis of diastematomyelia and associated congenital disturbances but also in planning and performing the necessary surgical treatment.

TREATMENT

Treatment of diastematomyelia consists in removal of the cord-transfixing elements and mobilization of the spinal cord. The early release of the lesion that fixes the spinal cord low in the spinal canal and keeps it from assuming its normal position in relation to the growth of the vertebral column is of utmost importance and allows normal spinal cord development and prevents increasing neurologic dysfunction. Thus, the operation is prophylactic rather than curative. It is also possible that, by early treatment, increasing spinal curvatures and more severe postural deformities may be avoided.

When resection of the midline septum does not fully mobilize the spinal cord, further fixation of the cord in its abnormal low position within the neural canal may be caused by a short, taut filum terminale. Section of the filum terminale then results in greater mobilization. A tight filum terminale has been reported as the cause of difficulty with locomotion and micturition in patients who also had spina bifida occulta and cutaneous defects.[13,14]

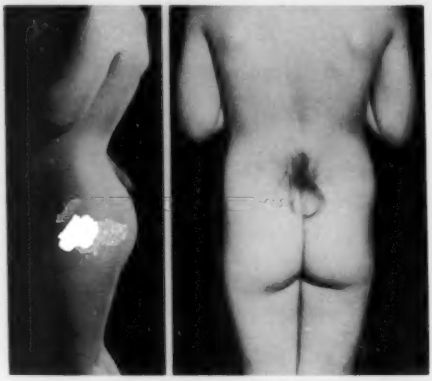

Fig. 1. *(Case 1)* Photographs of 5-year-old patient showing hypertrichosis and lordosis

CASE REPORTS

The following 3 recent cases are reported in detail to emphasize the variability of the symptoms and physical findings and to illustrate diagnostic problems.

Case 1. A 5-year-old girl was seen for the first time on January 10, 1956, because of intermittent low back pain and pain over the anterolateral aspect of the left thigh of six weeks' duration. Her parents reported that, during a period of pain lasting several days, the child would not care to play or walk and would remain in bed most of the time. She had presently been free of pain for five days and had no difficulty walking or playing. She had some questionable numbness of the left foot. Defecation and urination were apparently normal. The parents stated that the girl was born with a tuft of hair over the lumbosacral region. This hair kept on growing and reached 8 to 10 in. in length, and the hairy area became larger. Of interest was the fact that an older sister had died at birth with hydrocephalus.

At the time of examination, the child did not have any pain suggesting nerve root irritation; straight leg raising tests were within normal limits, and anterior flexion of the head did not produce pain. There was some questionable weakness in

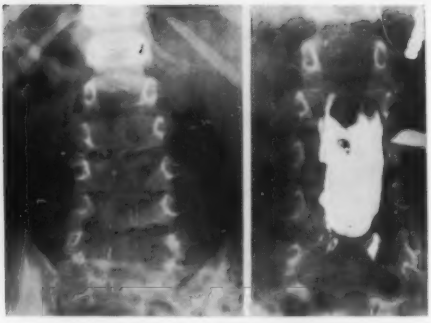

Fig. 2. (*Case 1*) Roentgenogram showing spina bifida, fusiform widening of lumbar spinal canal, and a suggestive bony spur arising from the posterior aspect of the body of the fourth lumbar vertebra. The myelogram outlines the central diastematomyelic defect over L4 and the inferior border of the arachnoidal cyst over the third lumbar body.

dorsiflexion of the left foot. However, all other movements were well performed, and there was no obvious muscle atrophy in the lower extremities or the gluteal region. The abdominal muscles contracted equally well. Beevor's sign was negative. The abdominal reflexes were brisk and equal. Pinprick was felt equally well over both lower extremities, the abdomen, back, and buttocks. Touch and position sense were within normal limits. The deep reflexes in the lower extremities were equally diminished, and she had a questionable Babinski sign bilaterally. Over the lower lumbar spine was an area of about 10 cm. in diameter, covered with long, silky hair (Fig. 1). A spina bifida involving the upper sacral segments and possibly the fifth lumbar vertebra could be felt. Palpation of the midline over the spinal defect produced localized pain most prominent over the second sacral segment. When standing, she had a scoliosis to the right in the lumbar region and a compensatory scoliosis to the left in the thoracic region. When bending forward, she would not move her lumbar spine and kept it in lordotic position. The paravertebral dorsolumbar muscles were tense, especially on the right side. She had no difficulty standing on tiptoe, heels, or either foot alone, and there was no abnormality of gait.

Roentgenograms of the spine showed spina bifida and marked widening of the interpedicular distances of the second to sixth lumbar and of all sacral vertebrae. There was also a marked discrepancy in the lateral view between the size of the sixth lumbar vertebral body and the first sacral, the latter being much smaller than the former. Several peculiar sites of calcification were observed within the lumbar and sacral spine; the most prominent one projected over the third and fourth lumbar vertebrae and suggested the possibility of a diastematomyelic spicule (Fig. 2).

It was thought at the time that the child's recent episode of pain may have been produced by diastematomyelia, an intraspinal lipoma, or an arachnoidal cyst. Myelography was advised but not carried out at the request of the parents.

She was seen again three months later. She had had no more pain and no further neurologic deficit. However, when standing or bending, she would still hold her lumbar spine rigid.

On June 11, the girl had occasional, sudden supraorbital headaches lasting about half an hour and accompanied by occasional lower abdominal pain. She had only rare back pain. The parents noticed that the child did not stoop but would squat down to pick up objects from the floor. They also reported that she would occasionally wet her panties during the day only. On examination, the right gluteal muscles appeared to be smaller than the left and the right patellar reflex was diminished when compared to the left. She had a lordosis of the lumbar spine with bilateral muscle spasms. Straight leg raising produced no pain, and there was no disturbance of gait and stance.

On January 30, 1957, the parents reported in a letter that the child had been well in the previous six months but, at times, had had back pain when bending forward. They also noticed that she had an area in her lower back which hurt when touched.

When seen again on August 20, she had had pain and muscle spasms in her lower back for three weeks after a fall. She had been complaining daily of back pain and would occasionally wake up during the night with severe pain. She also had occasional pain in the left leg. On examination, there was no obvious atrophy, motor weakness, or sensory loss in the lower extremities. The right patellar reflex appeared diminished as compared to the left. The Achilles reflexes were equal. The right Babinski sign was suggestively positive. The right buttock appeared smaller than the left. She had no sphincter disturbances. She would cry out when sitting up from the recumbent position because of pain in the low back and over the sacrum.

The child was then admitted to the hospital, and, on the following day, myelography was carried out under general anesthesia. The spinal fluid was clear and colorless and contained no cells and a total protein of 28 mg. per cent. Myelography revealed a complete block to the upward flow of contrast material at the level of the third lumbar body or the level of the superior border of the hypertrichosis. The block suggested an intradural tumor (Fig. 2). The caudal sac was seen to be pointed and irregular, and there was also a small filling defect superimposing the fourth lumbar vertebral body in the midline, suggesting a bony or cartilaginous spur. Lumbar laminectomy was carried out through a transverse incision. A

bony spicule, 9 mm. long and 8 mm. wide, divided the cord and was attached to the left rudimentary lamina of the third lumbar vertebra posteriorly (Fig. 3). The spinal cord extended to the upper border of the sixth lumbar vertebra and was held in this abnormal location by a taut filum terminale. The upper portion of the lumbar cord was covered and compressed by a posteriorly located arachnoidal cyst extending from the upper border of the second lumbar to the lower border of the third lumbar vertebra and producing a complete subarachnoid block. The bony spur and surrounding fibrous bands were resected, and the cyst was removed. The filum terminale was cut to allow complete mobilization of the spinal cord. The child's postoperative course was uneventful, and she was discharged on August 31 without further neurologic deficit.

Subsequently, the parents reported that the girl had been feeling fine since her discharge from the hospital and that she was an entirely different child. She was happier, more interested in her surroundings, and more ambitious, walked better, and ran more than before operation. Her lordosis had straightened, and she was able to bend forward to about 90°, moving her lumbar and thoracic spine well. Both patellar reflexes were absent. The Achilles reflexes were hypoactive. She had no muscle or sensory disturbances in the lower extremities and had good sphincter control. When seen last a year after operation, the child had occasional tickle in the midline of the lower back when sitting too long. The left patellar and the right Achilles reflexes were diminished. She had no Babinski sign. Motor and sensory examinations were normal. She had no atrophy. Stance and gait were normal, and the buttocks appeared equal in size.

In summary, this 5-year-old child's first symptoms were those of intermittent low back pain over a period of eighteen months and unwillingness to stoop forward. There was no obvious neurologic deficit, though the roentgenograms of the spine showed extensive spina bifida occulta and fusiform widening of the lumbar canal. There was also an area of lumbar hypertrichosis present since birth. Myelographic examination revealed a complete lumbar subarachnoid block that was produced by an arachnoidal cyst in the upper lumbar region and a midline defect at the fourth lumbar vertebral level, suggesting a diastematomyelia. These findings, together with a tight, short filum terminale, were verified at operation. Mobilization of the spinal cord relieved the patient's symptoms.

Case 2. A 10-year-old boy was referred to the State University of Iowa Hospitals on September 20, 1957, with a diagnosis of spina bifida, ulcerated right hammer toe, and bowel and bladder incontinence. The referring physician stated that new symptoms had occurred recently due to increased activity and growth.

This child was born with club feet and had been incontinent since birth. He was examined in Detroit at the age of 3 weeks, and lengthening of the Achilles tendons was done at the age of 2 years at the University of Michigan Hospitals. Spina bifida was diagnosed at that time, but surgical treatment was not considered indicated. An ulcer had been present over the right first toe since the child started wearing shoes. The ulcer had become infected and was worse in the past two months. The mother stated that she changed the boy's diapers every four hours. He was in fifth grade of public school, a good student, and active in sports.

Physical examination revealed a cooperative boy with mild abdominal discomfort. His height was 105 cm. When he stood, his body was flexed for-

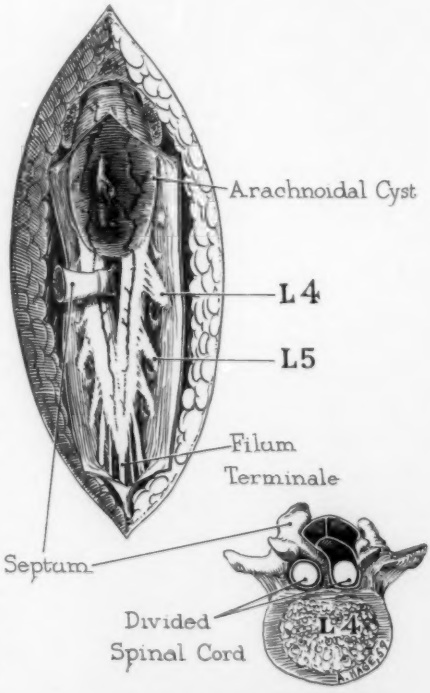

Fig. 3. (*Case 1*) Drawings of operative findings. [a] Bony and fibrous septum splitting the cord below the arachnoidal cyst. Notice the abnormally low location of the conus medullaris in the lumbar canal. [b] Cross-section view of pathologic findings with fusion of bony spur to rudimentary lamina and fibrous septum arising from dura posteriorly

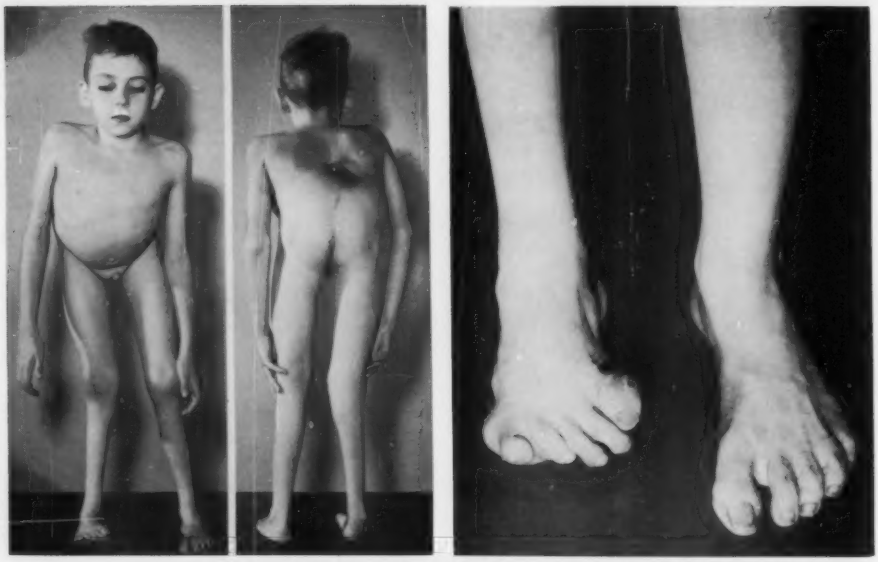

Fig. 4. *(Case 2)* Photographs of 10-year-old patient showing postural anomaly, hypertrichosis, atrophy of right leg, deformity of feet, and ulceration over anesthetic right first toe

ward at the hips and his hands reached down to below the region of the knees (Fig. 4). He had a protuberant abdomen with a rectus diastasis and an easily reduced right inguinal hernia. Respiration was mostly diaphragmatic. His trunk was short and deformed, but he was able to walk and move well. Mild lordosis extended from the upper thoracic region downward. A tuft of hair was present over the lumbosacral region in the midline over an area measuring 8 by 7 cm. Beneath this area of hypertrichosis, hard, bony, irregular prominences were palpable. The anal sphincter tone was reduced. Hard fecal masses were palpable within the entire abdomen. The lower extremities were atrophic, especially the right. Equinovarus deformities were present bilaterally. Trophic changes were present on the right foot and toes. An ulcer about 5 mm. in diameter, with a surrounding area of inflammation, was present over the dorsal aspect of the right first toe, which had a hammer toe configuration (Fig. 4). Both Achilles reflexes were absent; the other reflexes were within normal limits. Patchy hypalgesia was present over both lower extremities and abdomen.

Roentgenographic studies showed dextrocardia, multiple rib deformities and vertebral anomalies with hemivertebrae, and fusion of several dorsal vertebral bodies. Spina bifida involved the entire lumbar and sacral spine, and a large, midline abnormal bony mass projected over the dorsolumbar area. Intravenous pyelogram and cystogram showed a right hydronephrosis with hydroureter (Fig. 5). Renal studies suggested poor or no function on the left side, and there was difficulty in evaluating the function of the right kidney because of the residual urine in the right hydroureter. Laboratory examination revealed a blood urea nitrogen of 35 mg. per cent and serum phosphorus of 2.8 mg. per cent. Escherichia coli was cultured from the urine. It was also thought that this boy had a myelodysplasia and probable diastematomyelia, and myelographic examination was suggested but deferred by the parents.

Myelograms made a month later revealed a large filling defect in the lower thoracic and upper lumbar region in the center of an enlarged subarachnoid space (Fig. 5). There was splitting of the dye column for a distance of about 6 cm. Within the island, a large bony mass was visualized representing the cord-transfixing spur of diastematomyelia.

At operation, after exposure of a rudimentary dorsolumbar spine with spina bifida, a large bony prominence resembling a spinous process was encountered. It was connected with the right posterior arch of the twelfth dorsal vertebra by fibrous bands that compressed the dural sac. The defect in the posterior arches was most prominent at the eleventh and twelfth thoracic and first lumbar vertebrae. When the spinal canal was widely opened, the previously encountered bony prominence was found to split the dural sac into a large left and

a small right segment. The bony spur resembled a mushroom with a big head and a thin stalk. A posterior nerve root was seen leaving the left dural canal; it passed through a circular opening within the superior portion of the stalk of the bony spur to join other roots at an intervertebral foramen on the right side (Fig. 6). The bony spur was completely removed to its origin on the anterior aspect of the vertebral canal. At its base, it was 2 cm. long and 1½ cm. wide. The 2 halves of the spinal cord could be visualized over a distance of 6 cm.; they united above to form 1 cord and below to form a conus medullaris from which the cauda equina arose. The spinal cord was found to be anchored at the lower lumbar level to a short, thick filum terminale, which, in turn, seemed to be attached to another midline septum arising from the caudal portion of the spina bifida posteriorly. This septum was also resected, and the filum terminale was transected. The mobilized spinal cord was seen to migrate upward immediately after section of the filum terminale.

Postoperatively, the patient noted some tingling over the plantar surface of the left foot; he reported touch sensation in the extremities and moved them equally well. His blood pressure rose, varying from 150/120 to 170/130 mm. Hg, and he voided spontaneously in large quantities. On the second postoperative day, the blood pressure came back to 110/80; his blood urea nitrogen was 68 mg. per cent and creatinine, 2 mg. per cent. Within a few days, the blood urea nitrogen was 30 and the creatinine, 1.

At a check-up examination ten weeks after operation, he reported that he had been attending school, participating in sports, and doing well in his work. His sphincter control was still poor, and he continued to dribble urine. The blood urea nitrogen was 30 mg. per cent and the creatinine, 0.9 mg. per cent. The muscle strength in his lower extremities gradually improved. One year after operation, parents and patient stated that he had been growing and was able to stand straighter than before surgery. He had no pain or discomfort. At that time, he was wearing a penis clamp, which he opened every three hours during the day and which was removed at night. He stated that he had developed a feeling when his bladder was full and was able to urinate with pressure in sitting position. Sensation was present in all lumbar and sacral dermatomes. The hypertrichosis remained present in the lumbodorsal region.

In this case, diastematomyelia was associated with multiple bony anomalies of the spine and ribs, dextrocardia, feet deformities and ulcerations, and lumbar hypertrichosis. The anomalies produced disturbances in growth and physical development, incontinence of stool and urine, right hydroureter and hydronephrosis, left renal dysfunction, atrophy of the right lower extremity, and hypesthesia in both lower extremities. Myelographic examination and laminectomy confirmed the diagnosis of diastematomyelia; a taut filum terminale was also found. There was neurologic improvement following operation. Had this child been adequately examined and studied during infancy, his present physical handicap could perhaps have been avoided.

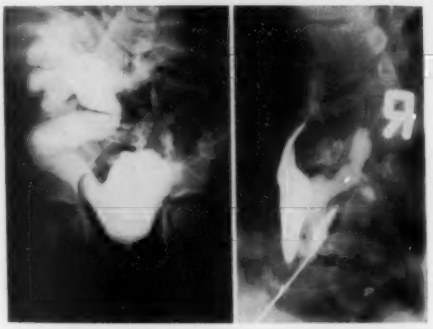

Fig. 5. (*Case 2*) Delayed cystogram showing dilation of right ureter and renal collecting system. Notice underlying vertebral anomalies. The myelogram shows splitting of the dye column in the lower thoracic region around a large bony spur.

Fig. 6. (*Case 2*) Photograph of operative view showing stalk of large bony septum dividing spinal cord and dorsal nerve root passing through spur from left half of cord to join roots on right side

Case 3. This infant boy was first seen at the State University of Iowa Hospitals on June 30, 1955, at the age of 12 days, because of unsatisfactory development. He had a large, bulging, lumbodorsal myelomeningocele that appeared to

ESSENTIAL FEATURES IN 8 CASES OF DIASTEMATOMYELIA

Case*	Age	Sex	Symptoms	Cutaneous defects	Skeletal deformity	Neurologic defect
1	3½ yr.	F	Leg pain	Hypertrichosis	——	——
2	1½ yr.	M	Ulcerated toe, dragging left foot	Hypertrichosis, dimple	Small left foot	Motor and sensory, left foot and toes, absent left patellar and Achilles reflexes
3	6 mo.	F	Left foot deformity	Hypertrichosis, dermal sinus, bony protrusion	Left club foot (equinovarus), small left foot	Diminished left patellar and Achilles reflexes
4	1 yr.	F	Dragging right foot	Hypertrichosis, dimple	Right club foot (equinovarus)	Weakness right leg
5	1 mo.	F	Myelocele	Myelocele	Multiple spinal, bilateral club foot (calcaneovarus)	Paraplegia
6	5 yr.	F	Back pain	Hypertrichosis, dimple, bony protrusion	Lordosis	——
7	10 yr.	M	Ulceration toe, incontinence	Hypertrichosis, bony protrusion	Multiple spinal, kyphosis, lordosis, bilateral club foot (equinovarus), right hammer toe	Atrophy right leg, hypalgesia, incontinence
8	4 mo.	M	Myelocele	Myelocele	Bilateral club foot (calcaneovarus)	Paraplegia

*Cases 1–5, previous report[7]
Cases 6–8, present report

RADIOGRAPHIC AND MYELOGRAPHIC FINDINGS

Case*	Radiogram	Myelogram
1	Spina bifida, spur	T10 midline defect
2	Spina bifida	Split T9-L1
3	Spina bifida, spur	Split L2-L3
4	Spina bifida, T12-L1 spur	Split T12-L1
5	Spina bifida	——
6	Spina bifida, spur	Block and cyst L3, split L4
7	Spina bifida, spur	Split 6 cm., dorso-lumbar
8	Spina bifida, spur	——

*Cases 1–5, previous report[7]
Cases 6–8, present report

be superficially infected. The head circumference was larger than normal, and the anterior fontanelle was large but not tense or bulging. Also, a cranial defect extended along the entire sagittal suture. Both lower extremities were flaccid, showed no movement, and had no reflexes. There was urinary and stool incontinence. This child was the result of the first pregnancy of an 18-year-old mother. The mother had had vomiting for eight months during an otherwise uncomplicated pregnancy. She claimed not to be aware of any central nervous system anomalies in either her or her husband's family. Conservative therapy was recommended for the treatment of the myelomeningocele infection.

The child was admitted to the hospital at the age of 4 months. The myelomeningocele appeared clean. The hydrocephalus had greatly increased, and both large anterior and posterior fontanelles were tense and bulging. Flaccid paraplegia with foot deformities was noted. Roentgenograms showed the characteristic fusiform widening of the midthoracic spinal canal with a dense midline shadow overlying the seventh, eighth, and ninth dorsal bodies, suggesting a diastematomyelic bony septum (Fig. 7). The intervertebral space between the eighth and ninth vertebral bodies was narrowed. The posterior neural arches were defective in the entire lumbar and dorsal regions. The obvious presence of myelomeningocele and hydrocephalus caused the diastematomyelia to be overlooked and not diagnosed. After ventriculographic studies and dye tests, the myelomeningocele was excised and, at the same time, a ventriculoperitoneal shunt was performed. The hydrocephalus did not seem to drain adequately, and the head kept on increasing in size. Four weeks after operation, the ventriculoperitoneal shunt was revised and the omentum resected. Following this procedure, the head size diminished. Ventricular fluid protein was 145 mg. per cent.

At the time of repair of the myelomeningocele, an anomalous portion of the lumbar cord was found attached to the dome of the myelocele sac and was removed along with the sac. The portion of the cord visible within the spinal canal above the spina bifida did not appear normal, and a catheter could not be passed upward within the subarachnoid space for a distance of more than 4 cm. from the operative site. It was also noted that compression of the fontanelle did not produce a flow of spinal fluid in the operative area.

The shunt appeared to be working satisfactorily until May 2, 1956, when the child showed slight increase in head size, a disparity in the size and reaction of the pupils, and spontaneous lateral nystagmus. It was thought that the child probably had an Arnold-Chiari malformation. Four months later, the child was vomiting and the head had again increased in circumference. There was severe ataxia of the eye balls. Ventriculographic studies and dye tests were repeated, and the ventriculoperitoneal shunt was revised. The peritoneal end of the shunting tube was found to be completely plugged. The ventricular fluid protein was 63 mg. per cent. Ten days later, the child was readmitted because of disruption of the lateral thoracic incision through which the tube had been inserted. However, again the head circumference had increased in size and the ventriculoperitoneal anastomosis was revised. The ventricular fluid protein had been 152 mg. per cent. The shunt appeared to work satisfactorily for five weeks, when again the child showed increase of his hydrocephalus and was vomiting. The ventriculoperitoneal shunt was revised on January 14, 1957, for the fourth time. On March 28, the head had not increased in size. However, there was some flaccidity in both upper extremities, atrophy of the neck muscles and marked spontaneous nystagmus. The child had also had some vomiting, was irritable, and seemed to have pain about the head and neck. A tap showed that the ventricular fluid was slightly xanthochromic and sterile but that the protein was 232 mg. per cent. The pressure was not elevated, and the cell count was normal. The child died suddenly on April 24, at the age of 22 months.

Autopsy revealed a large internal hydrocephalus with atresia of the aqueduct, absence of the vermis with malformation of the cerebellar hemispheres, an Arnold-Chiari malformation, and residual myelomeningocele with a diastematomyelia in the lower thoracic region. The cervical cord was wide and big and contained a large central cavity that measured about 15 mm. in diameter. In the lower thoracic region, the cord was split but both halves were contained in a single dural canal. The length of the diastematomyelic defect measured 2.8 cm. A bony ridge arose in the midline from the posterior aspect of the bodies of the seventh, eighth, and ninth dorsal vertebrae, and the cord-transfixing spur originated from the superior portion of the ridge (Fig. 8). The cord started to divide into 2 separate segments approximately 1 cm. above the superior edge of the spur. Each of the 2 cord segments contained a widened central canal that was discolored slightly yellow. The left half of the spinal cord was circular and measured 6 mm. in diameter. The right half was larger but more oval in shape, measuring 10 mm. in diameter. The central canal on the left side was round and, on the right side, was irregular in shape and appeared more like a horizontal slit

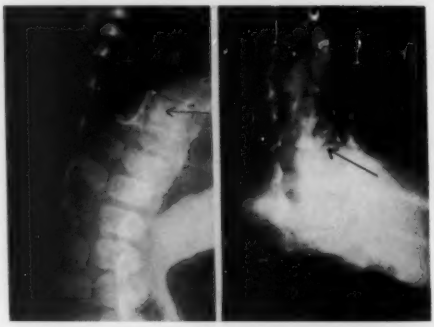

Fig. 7. (*Case 3*) Roentgenograms showing the extensive defect of the posterior neural arches and the midline bony septum in the midthoracic region. The bony spur is exceptionally well seen in the lateral projection.

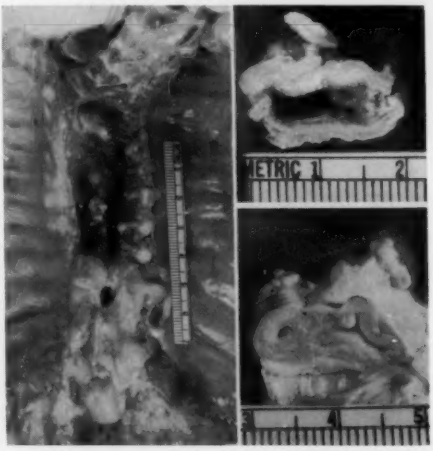

Fig. 8. (*Case 3*) Autopsy findings. [a] Bony ridge in spinal canal, with split in retracted spinal cord. [b] Hydromyelia of upper thoracic cord. [c] Cross section of both cord segments at the site of diastematomyelia

(Fig. 8). No union of the split portions of the cord could be detected below the diastematomyelia and above the scar of the repaired myelomeningocele.

In this case, the diastematomyelia with hydromyelia in the lower thoracic region remained undiagnosed and unsuspected until autopsy. This child had a myelomeningocele and a hydrocephalus and presented many features similar to those of the case reported by Weil and Matthews.[15] There was no hypertrichosis. Roentgenologic characteristics of diastematomyelia were evident but overlooked in the presence of the obvious myelomeningocele and hydrocephalus. Several attempts to drain the hydrocephalus were only temporarily successful. At autopsy, an Arnold-Chiari malformation and other cerebellar malformations were also encountered.

SUMMARY

The symptoms and clinical findings of 3 new cases of diastematomyelia and 5 previously reported cases are discussed. Localized hypertrichosis characterized by long, soft hair in the midline of the back, usually covering the region of the underlying spinal anomaly, was noted in 6. Associated with it were congenital dermal sinus, lipoma, skin dimples, and abnormal bony protrusions; 2 cases had a thoracolumbar myelomeningocele.

The common symptoms were related to disturbances in locomotion; 6 of the patients had congenital anomalies of one or both feet. In 2 instances, intermittent low back pain associated with occasional pain in the lower extremities was the only sign. Neurologic disturbances were present in 6 and consisted of impaired function of one or both lower extremities with weakness, atrophy, reflex and sensory changes, and occasional impairment of rectal and bladder function. Although the obvious cutaneous and skeletal anomalies had been present since birth, the neurologic disorders became more evident when the patients started to walk.

The diagnosis of diastematomyelia and its exact location depends upon radiologic and myelographic determinations. Spina bifida occulta with associated fusiform widening of the spinal canal and other vertebral anomalies were always present. Myelographic studies outlined the characteristic midline bony, cartilaginous, or fibrous septum that divided and immobilized the spinal cord over several segments in the thoracic or lumbar region. In 2 instances, a taut filum terminale had to be sectioned at the time of removal of the cord-transfixing septum in order to fully mobilize the spinal cord.

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Procaine-oil-wax pallidotomy for double athetosis and spastic states in infantile cerebral palsy

Report of 80 cases

H. Narabayashi, M.D., H. Shimazu, M.D., Y. Fujita, M.D., S. Shikiba, M.D., T. Nagao, M.D., and M. Nagahata, M.D.

STUDIES WITH STEREOTAXIC pallidotomy for athetosis using injections of procaine in oil-wax, first begun by the authors[19] in June of 1951 in the Department of Neurology and Psychiatry, Tokyo University, were based on the hypothesis, originally suggested by Jacob,[15] Foerster,[25] Vogt and Vogt,[33] and others in the period from 1920 to 1930, that there was an antagonistic relation between the striatum and pallidum, so that pathologic degenerative processes within the striatum released the pallidum to a state of hyperfunction. The choreoathetotic abnormal movement, the so-called striatal symptom, was considered to be a manifestation of this hyperfunctional activity of the pallidum, for which a pallidal operation might be postulated to be effective. This should be called the "classical pallidal theory" of the pathophysiology of abnormal movements. Several papers on the pallidal operation for choreoathetosis or dystonia have appeared by Spiegel and Wycis,[26–30] Guiot and Brion,[10] and Cooper,[4–6] indicating that the procedure, i.e., pallidotomy or pallidoansotomy, is effective for these disorders.[25] But the results differ, and the neurophysiologic analysis seems to be indefinite.[18]

The authors' experiences in stereotaxic pallidotomy for athetosis increased as the procedure became more commonly used for parkinsonism. By analyzing the pre- and postoperative electromyograms of both diseases, the authors thought that a common mechanism might be formulated to explain the results of the operation. This will be discussed later.

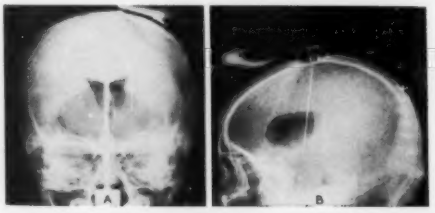

Fig. 1. Roentgenograms of the skull after injection of air in the cerebral ventricles and placement of pallidotomy needle to show the position of the injection

METHODS

The stereotaxic technic used by the authors has been previously described in detail.[19,21] The instrument has been modified several times. The present sixth model is fixed to the skull with reference to a base line in the inferior orbitoauricular plane. The point to be destroyed is ascertained on the pneumoencephalogram by reference to the foramen of Monro or the anterior commissure.[1,32] The needle position is further checked under 3-dimensional x-ray control during the procedure (Fig. 1). For destruction of the nuclei, the authors inject procaine in oil-wax only, since the earlier use of electrocoagulation did not give satisfactory or consistent results. The injected mass is about 0.4 to 0.8 cc. in most cases, which is

From the Department of Neuropsychiatry, Juntendo Medical School, the Department of Neurophysiology, Tokyo University Medical School, and the Departments of Neuropsychiatry and Pediatrics, Tokyo University Hospital.

TABLE 1
AGE DISTRIBUTION

Age (years)	*Number of cases*
Over 20	32
11 to 20	25
5 to 10	23

TABLE 2
PRESUMED ETIOLOGIC FACTORS

Premature birth, prolonged labor, asphyxia, or icterus neonatorum gravis	44 cases
Febrile episode with convulsive disorders in infancy	31 "
Cerebral contusion in infancy	2 "
Unknown	3 "
Total	80 "

considered to be enough to block nuclear function and to remain semipermanently in the site injected as an encapsulated foreign body.

Even though the stereotaxic technic is considered accurate, it still is a blind procedure. The operative lesions are oval or nearly round, from 0.5 to 1 cm. in diameter. It is obviously impossible to produce a strictly selective lesion along the complete width and length of the pallidum, though a complete miss of the pallidum is almost impossible. Accordingly, it seems reasonable to define the goal by the genetic term "pallidum" rather than by more specific terminology such as the internal segment. The possibility of neighboring structures other than the pallidum being involved should naturally be considered in analyzing the mechanism involved in the procedure.

CASE REPORTS

A total of 80 cases that have been followed from six to seventy-eight months postoperatively are reported. Age distribution of the patients (Table 1) varied from 5 to 34 years. About half the patients had an associated spastic infantile cerebral palsy. Etiologic factors included premature birth, asphyxia at birth, prolonged labor, icterus neonatorum gravis, infectious infantile fevers including verified Japanese B encephalitis, and intestinal intoxication (Table 2). Results of operation are given in Table 3, and 8 illustrative cases are described in detail.

Case 1 (serial No. 1). T.K., male, aged 19; diagnosis, double athetosis. The patient's gestation was reported as having been uneventful; his delivery at full term was noninstrumental and apparently normal. The patient grew normally until one summer at the age of 6 he had an episode of high fever and somnolence for two weeks. Thereafter, involuntary movements of the facial muscles and tongue appeared and gradually involved the upper and lower extremities on both sides.

On admission, a slight weakness of the right upper limb and right facial muscles was noted. During involuntary movement, the muscle tone of the affected parts was increased. The dyskinesia, of an athetoid type, was most severe and typical in the face and right upper limb, with grimacing of the face and writhing movements of the extremities. Speech was slow and lalling. Because of the abnormal movements and positional irregularities of neck and scapulohumeral muscles, the patient could not sit quietly, write, or hold a spoon. The

TABLE 3
RESULTS OF PALLIDOTOMY

Grade of improvement	*Markedly improved*	*Fairly good*	*Slightly improved*	*Not improved*
1. Double athetosis without spasm				
Over 11 years (28 cases)	9	5	10	4
5 to 10 years (6 cases)	1	4	1	–
2. Double athetosis with spasm				
Over 11 years (9 cases)	–	5	2	2
5 to 10 years (19 cases)	2	10	5	2
3. Hemiathetosis (18 cases)	5	9	4	–
Total (80 cases)	17	33	22	8
Mortality—nil				

One patient had a transient (three weeks) capsular hemiplegia.

athetosis was aggravated by emotional tension. The lower extremities were affected less than the upper, but the gait was slow and unsteady.

The cerebrospinal fluid was normal, and a pneumoencephalogram showed slight enlargement of both ventricles with relative displacement of the third ventricle to the left, suggesting a degenerative process in the left basal region.

Operation was carried out on June 1, 1951, with an injection of 1 cc. of procaine in oil-wax suspension through a needle stereotaxically inserted into the pallidum after injection of a small amount of an aqueous solution of procaine, which predicted a successful block of the nucleus.

Postoperatively, the result was so favorable that the patient became able to write, hold a spoon, and talk much more clearly. Ten months later, he passed a difficult entrance examination to a technical school, which he could not have hoped to have done preoperatively. However, the postural abnormality of the extremities seemed more difficult to improve than the abnormal movement itself.

These results encouraged further study.

Case 2 (serial No. 7). S.A., male, aged 25; diagnosis, postinfectious double athetosis. The patient, of healthy stock, was delivered normally at full term. No disturbances of mental or physical development were noted until the age of 4, when the patient suffered from severe ekiri, with high fever and generalized convulsions followed by coma for more than ten days. (Ekiri is the Japanese name of shigellosis in childhood.) Following this illness, a state of apathy, hypokinesia, and hypersalivation appeared. About five years later, grimaces of the face and mumbling movements began to appear. Within two years, choreoathetotic movements involved all skeletal muscles, causing difficulties in speech and swallowing and making walking impossible without help.

The abnormal movement was not only athetotic but combined with choreic, rapid, incoordinated jerkings on both sides. The tendon reflexes were normal at the time of admission. The left pupil was miotic, but both pupils were round and responded through a small range to light. Speech was lalling and sometimes explosive.

Left stereotaxic pallidotomy was performed on March 12, 1954, 0.8 cc. of the mixture of oil-wax with procaine being injected, and was followed by dramatic abolition of the abnormal movements on the contralateral side of the body without any sign of capsular palsy. Right pallidotomy two weeks later produced a similar effect.

Postoperatively, alleviation of the choreoathetotic movements was so complete that the patient could walk steadily without help, feed himself, and write. Facial grimacing was also reduced and appeared only at the time of emotional excitement (Fig. 2A and B). Improvement in speaking was also noted.

Case 3 (serial No. 19). K.K., male, aged 19; diagnosis, right hemiathetosis. The patient, of normal parents, had an instrumental prolonged delivery followed by asphyxia for about thirty minutes. He walked unsteadily at the age of 2. Involuntary movement was observed then and became more noticeable as he grew. After he had repeated generalized convulsive seizures at the age of 3, the involuntary movements became much more severe. His abnormal movements were restricted mainly to the right side of the body, though the left side was very slightly affected. The right hand was not used for holding a spoon, writing, or even holding a ball. A left sided pallidotomy was carried out on July 10, 1956, with injection of 0.65 cc. of oil-wax without procaine. Immediately after the operation, the athetotic movements of the face and extremities were abolished almost completely, resulting in a marked improvement in involuntary activity such as holding objects, writing, and walking. Even his speech became clear. Improvement has been continuous, and, at present, he seems almost normal in his everyday activities (Fig. 2C and D).

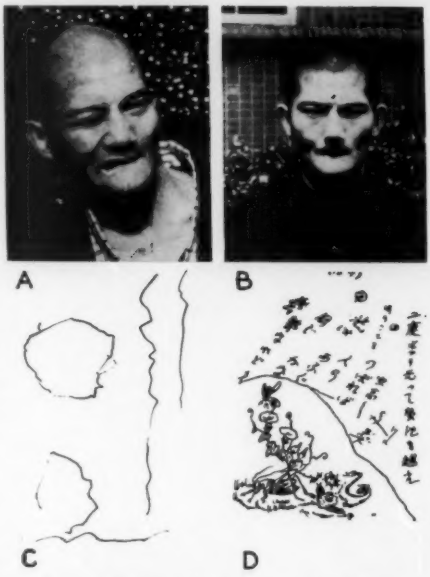

Fig. 2. Photographs show the involuntary grimacing of the face [A] before operation and its relief [B] after operation. The lower sketches are the handwriting of patient 19 [C] before and [D] after operation.

Case 4 (serial No. 28). M.U., male, aged 6; diagnosis, infantile cerebral palsy with athetosis. The patient had a normal birth and development until the age of 2 years, when, after two days of febrile convulsions, he began to have athetotic,

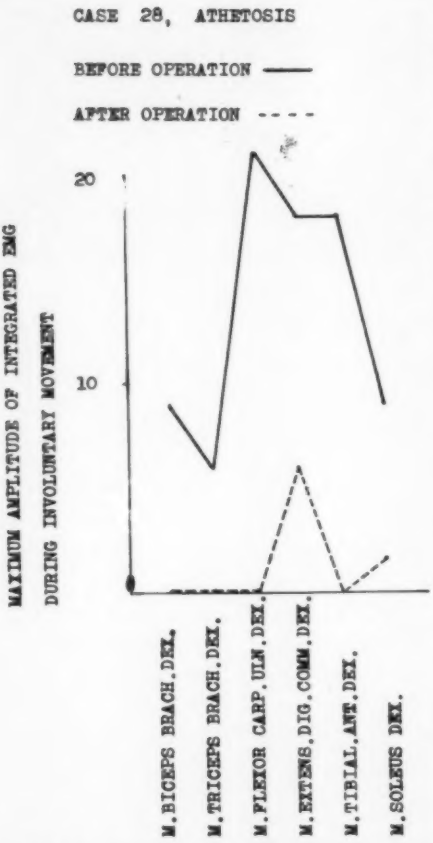

Fig. 3. Graph to show the improvement in the electromyogram during involuntary movements after operation

dystonic movements of both sides. The abnormal movements were so severe in his upper limbs that sitting and standing were impossible. He could not break bread or even bring it to his mouth. Speech was almost impossible.

A pallidotomy was performed on the left side and then on the right side three weeks later. On both sides, improvement occurred. The involuntary contractions of the facial muscles were abolished, and the athetotic movements of the limbs were reduced as shown in electromyograms (Fig. 3). Postoperatively, the patient was able to feed himself and walk with a little help.

Case 5 (serial No. 68). Y.F., male, aged 8; diagnosis, cerebral palsy due to kernicterus. The patient had a normal delivery at full term, but, on the fourth day, icterus neonatorum gravis developed, which continued for about forty days with high fever and cyanosis. Clinically, the patient had all the features of kernicterus.

The patient was unable to hold up his head or sit. Though his understanding was good, he could not speak. Athetotic movements were present in both upper extremities and the face. This patient had a very severe cerebral palsy with athetosis (high grade rigidospasm). He lay on a bed unable to perform any skilled act.

A left sided pallidotomy was performed on July 28, 1958, and a right sided pallidotomy on August 19, resulting in marked improvement. The right leg, which had been hyperextended, could be flexed voluntarily. The severe hypertonic "rigidospasm" was reduced in all skeletal muscles, so that passive and voluntary movements were possible. Facial expressions such as a smile became more natural, and feeding was easier than preoperatively. The patient became able to hold objects in his hands and to bring them to the mouth.

The preoperative electromyogram of this case showed marked fluctuation of the spontaneous discharges corresponding to the clinical athetotic movements. Stretching the muscle at the time of these basic discharges augmented the reflex discharges, which persisted for many seconds. However, stretching the muscle at the phase of electrical silence induced no electrical discharges.

After pallidotomy, the spontaneous fluctuating discharge was reduced greatly, and muscle stretch produced no effect at any phase (Fig. 4).

Case 6 (serial No. 65). R.M., female, aged 6; diagnosis, cerebral palsy with athetosis. After a normal delivery at the tenth month of gestation, the patient had a severe icterus that lasted for about three weeks with vomiting and fever. Subsequently, she presented the clinical picture of kernicterus.

On admission, she had spastic crossed legs with everted feet, hyperextended arms, and flexed fingers. No volitional postural movement such as sitting or turning over in bed was possible. The patient appeared to understand her mother's speech relatively well.

Pallidotomy was carried out on the right side on June 10, 1958, with injection of 0.3 cc. of oil-wax and on the left side on June 22, 1958, with 0.4 cc. After surgery, the feet were improved so that the patient could stand with a little help. Phonation and the posture of the arms and hands were improved, too.

In the electromyogram, stretching the left triceps brachii produced a marked increase in the length of the electrical discharges but stretching the left biceps produced no reflex discharges and the latter muscle showed a tendency to parallel the electrical activity of the triceps. This disorder of reciprocal innervation is often seen in athetosis, as pointed out by Hoefer and Putnam.[13] Postoperatively, the stretch reflex was very exceptionally

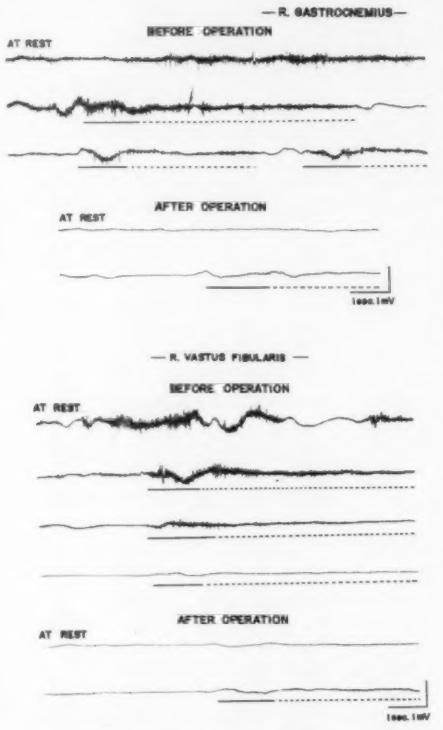

Fig. 4. Electromyograms to show the fluctuating rigidospasm before and after pallidotomy

obtained and only at the initial phase of the stretch. The long-lasting discharges were abolished selectively, leaving the initial phasic one. From the left extensor digitorum communis, fluctuating discharges occurred preoperatively at rest, with exaggerated discharges at the initial phase of stretching. After pallidotomy, these involuntary fluctuating discharges were reduced and the stretch discharge became less manifest. The same observation was made on the left flexor digitorum communis muscle.

Case 7 (serial No. 58). H.K., female, aged 16; diagnosis, right hemiathetosis. This girl had a normal birth at full term and developed normally until her fifth year, when she suffered from a fever, went into a comatous state for a few days, and had convulsive seizures. Upon her recovery, she was noted to have a right hemiplegia and right sided athetotic movements. The palsy disappeared within several months, but the abnormal movements remained. The patient's speech, intelligence, and personality seemed unchanged.

Writhing and incoordinated athetotic movements of the right arm were so severe that she could not use her right hand for feeding herself or for writing. Grasping objects was almost impossible due to overcontraction of the fingers.

A left pallidotomy on April 29, 1958, improved the athetosis so that the patient could hold a spoon and pencil and perform some voluntary movements with the hand.

In the electromyogram, the long-lasting afterdischarges of the stretch reflex were reduced with little change in the initial discharges (Fig. 5). Voluntary relaxation became easier postoperatively, and an ankle clonus formerly obscured by the excessive tonic activity became apparent after surgery.

Case 8 (serial No. 63). J.S., male, aged 9; diagnosis, infantile cerebral palsy. The patient, the second born of twins, had some asphyxia due to prolonged birth of his twin, and, shortly after, icterus neonatorum gravis developed. His mental development was severely retarded. On admission, he was unable to make any voluntary, skilled act; even swallowing or biting was impossible so that he was fed liquids. He could understand only a few words of his mother. All 4 extremities, especially the right arm, had severe athetotic movements. Although little change was expected to

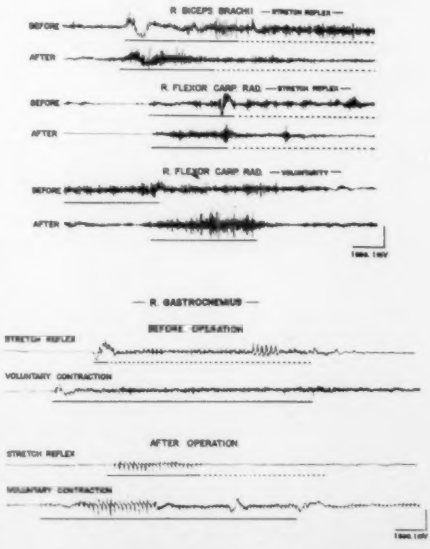

Fig. 5. Electromyograms to show the reaction to stretch and voluntary innervation before and after pallidotomy

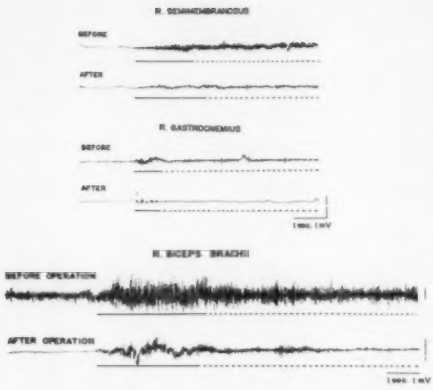

Fig. 6. Electromyograms illustrating the reaction in a case of athetosis to stretch of the semimembranosus and gastrocnemius muscles and to rigidospasm in the biceps muscle before and after pallidotomy

result from surgery, there was an obvious lessening of the rigidity of the muscles, accompanied by clinical improvements. Six months after bilateral pallidotomy, the patient could sit on a chair with his knees flexed, could hold a spoon, and smiled almost naturally. The most remarkable change was observed in the right leg, which preoperatively had such severe adductor spasm that it crossed the left. It was improved to the extent that crossing was minimal, and the posture of the foot improved much.

Preoperatively, electromyogram of the semimembranosus muscles presented marked stretch discharges; postoperatively, these discharges were reduced greatly. In the right gastrocnemius muscle, the tonic after-discharges disappeared after pallidotomy, but the initial discharges of the stretch reflex remained and clonus appeared (Fig. 6).

DISCUSSION

A total of 80 cases of unilateral or double athetosis of various etiologies, often combined with Little's disease, were treated by stereotaxic pallidotomy.

As shown in Table 3, marked improvement, both subjective and objective, was obtained in 17 cases (21.2%), fairly good results in 33 cases (41.2%), and slight improvement in 22 cases (27.5%). So, beneficial effects were observed in 50 cases (62.5%).

Pallidotomy seems to be more effective for athetotic patients without spastic signs, clinically and electromyographically, than for those with marked spastic signs (see Table 3[1]). Hemiathetosis has a better prognosis than double athetosis. It should be noted that the patients with severe athetosis or severe spastic states were not much improved by the pallidal operation, possibly due, in part, to secondary changes in muscles and joints.

The improvement was observed in the contralateral skeletal muscles of the face, trunk, and upper and lower extremities. Athetotic movements disappeared or became markedly diminished. The facial expression became more calm, quiet, and natural as the previous grimaces and contortions abated. The preoperative dysarthric speech, perhaps due to involuntary and incoordinated lip and tongue movements, became clear and distinct after operation.

The irregular spasmodic and writhing involuntary athetotic movements of the trunk and extremities disappeared or diminished. With improvement, voluntary purposeful movements associated with everyday living and more highly coordinated acts became possible or easier.

The seemingly hypertonic state of the muscles, as manifested by the hyperextended fingers and elbows, twisted trunk, overcontracted or hyperextended knees, and everted feet, was improved and the "hypertonus" of the muscles decreased. These changes suggested that the beneficial result of the operation was related to an alteration in the degree of muscle tone. This will be further discussed on the basis of the electromyographic analysis of the pre- and postoperative condition of the muscles.

In clinical neurology, the so-called spastic, hypertonic muscles indicate a state of exaggerated stretch reflexes.[16,17] On electromyographic examination, these reflexes are demonstrated by increased action potentials of the stretched muscles. These responses can be divided into 2 groups by the subsequent course of the discharges. The first group shows a tendency for a rapid reduction of the action potentials within a few seconds, despite the continued stretching of the muscle. This is called the "adaptation phenomenon." The second group shows little or no tendency for adaptation. An example of the latter is the rigidity of parkinsonism and of the former, the spasticity after cerebral hemorrhage.

In athetosis, however, the spontaneous action

potentials of muscles fluctuate, corresponding to the occurrence of involuntary movements. It is, therefore, not always as easy to examine the stretch reflex in athetosis as it is in a case of parkinsonism.[12–14] But examination is possible when the progression of the abnormal contraction is slow or when a relatively constant state continues for a sufficient period. Generally speaking, the stretch reflex in athetosis is not constant but depends upon the state of the muscle before being stretched. The results vary from case to case and from time to time: [1] The stretch reflex is *often* absent when the muscle examined is electrically silent. [2] The stretch reflex will be present and exaggerated when the background discharges are marked, the quantity of these reflex discharges being roughly parallel to that of the amount of basic discharges produced by the athetotic movement. If the muscle is constantly stretched, the augmented discharges usually continue for more than several seconds or fluctuate about a mean that is greater than the background activity before being stretched. In many cases of athetosis, the general tendency for rapid adaptation as seen in spastic states due to cerebral hemorrhage is not found. This pattern of response to stretch suggests that the mechanisms producing athetotic movements may be similar to those of parkinsonian rigidity, at least during the appearance of the fluctuating basic discharges.

In some cases of athetosis, the so-called hypertonia or hypotonia was gauged by the presence or absence of the spontaneous discharge. But, in the authors' series, stretching of a muscle often elicited reflex discharges during a period of electrical inactivity. This, then, was felt to be a more sensitive indicator for "hypertonia" than the appearance of spontaneous discharges. On the other hand, the so-called "hyperkinesia," e.g., Sydenham's chorea, is the involuntary discharge itself, which originates independently of stretching of the muscle and which, indeed, often results in suppression of the spontaneous action potentials of hyperkinetic muscles. Therefore, hypertonia or elevated muscle tone, exemplified by exaggerated stretch reflex, is considered to be responsible for athetosis but not for the hyperkinetic movement. Athetosis, in most cases, should be considered not as "hyperkinesis itself" but as the phenomenon caused by the fluctuating elevation of muscle tone. This concept implies not only a difference in definition but also, and more important, in clinical significance, on which the results of pallidal operations are predictable.

In the authors' previous papers,[20–23] the specific effect of pallidal operations on the rigidity of parkinsonism, in contrast to its lesser influence on tremor, was noted and the important role of the pallidum in producing and accentuating the "hypertonic" state of rigidity was suggested. Figure 7 shows the electromyograms of the typical case of parkinsonism before and after operation. The spontaneous discharge characteristic of rigidity, reinforced by stretching the muscles, continues without adaptation throughout the whole course of the constant stretch and after pallidotomy is minimal.

The rigidity-like hypertonic state in athetosis mentioned above can also be markedly improved by the same operative procedure on the pallidum that alleviated parkinsonism. This again suggests that some components of athetosis might have something in common with parkinsonian rigidity. After operation, the spontaneous fluctuating electrical activity and the stretch reflex discharges are both diminished markedly, paralleling the clinical improvement. Reflex discharges on stretching in the electrically silent phase are also abolished, in contrast to their prominence preoperatively.

Furthermore, many cases of athetosis were associated with Little's disease and showed the 2 electromyographic characteristics of hypertonus together, one with a tendency for adaptation and the other with a lesser tendency, as described in Figure 5. In this group, at the initial phase of muscle stretching, the reflex

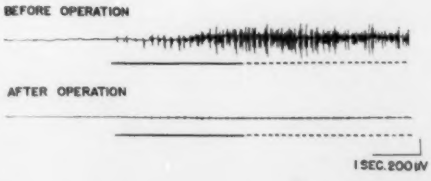

Fig. 7. Electromyograms to show the effect of pallidotomy on parkinsonian rigdity. Left extensor digitorum communis muscle

discharges increased markedly and then remained almost constant at a level lower than the initial phasic one or gradually decreased over a relatively long period. This type of combined reflex discharges is termed by the authors the "rigidospastic type." Generally speaking, blocking of the pallidum in this group was more effective in reducing the tonic reflex discharges than the initial phasic reflex discharges. As often observed, the initial reflex discharges remained almost unchanged (Fig. 5), but in other cases they were reduced to some degree, corresponding to the disappearance of the tonic after-discharges (Fig. 6) and resembling observations in the previous report that tremor could be influenced by pallidotomy only with improvement of rigidity. As for clonus, it was little influenced by pallidotomy or even became manifest as a result of diminution of the coexistent rigidity (Fig. 5). All these facts suggest that, in athetosis, the globus pallidus plays a role in the production or accentuation of a hypertonic state similar to parkinsonian rigidity but is not responsible for clonus or the initial phasic discharges of the stretch reflex.

But, in 8 cases (10%), the operation was not effective, though the clinical picture resembled typical athetosis. This percentage is very important. Neuropathologic studies of athetosis suggest various etiologies, which might result in different neurophysiologic mechanisms producing similar symptoms for which pallidotomy is ineffective.

The concept "pyramidal" and "extrapyramidal" should rightly be reconsidered,[11,24] as pointed out by Bucy.[2,3] Granit[7–9] proposed a theory to explain this concept physiologically. This paper is only an attempt to explain the mechanism of hyperkinesis, specifically as seen in athetosis.

The method of the authors of dividing the stretch reflex into 2 types according to its pattern, tonically long lasting and phasically adapting, and of relating them to the efficacy of pallidal operations is felt to be useful in understanding the large group of extrapyramidal disorders. This paper relies upon clinical observations and hence precise analyses are not warranted. But the role of "hypertonia" in the so-called extrapyramidal disorders is more important than formerly believed and in part, at least, the basis for these "hypertonic" states may be related to the globus pallidus.

SUMMARY

Experiences with procaine-oil-wax pallidotomy in 80 cases of unilateral or bilateral athetosis are reported, with electromyographic analysis before and after the operation. Notable clinical improvement was obtained in 62.5% and slight in 27.5% of the cases; improvement in everyday activity and voluntary movement occurred in various degrees. In electromyograms, stretch reflex discharges of the tonic type, which are thought to be the essential basis for athetotic movement, are reduced notably by the procedure. This suggests an explanation of choreoathetosis as a disorder of muscle tone and emphasizes the importance of the pallidum in regulating the level of muscle tone.

The authors are indebted to Dr. T. Okuma for his assistance in the early period of this research.

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Central hemorrhagic encephalopathy of early infancy

Report of 3 verified cases suggesting the genesis of infantile cystic degeneration in a paranatal anoxic disorder

Cyril B. Courville, M.D.

IN THE PAST CENTURY, a peculiar widespread cystic degeneration of the encephalic white matter of infants has come to be recognized. The lesion is obviously a chronic one, for both its gross and microscopic characteristics indicate the end-stage of a process, the true nature of which has been widely debated. The term "cystic" is a misnomer, for the lesion consists essentially of a widespread subtotal cavitation that replaces the white matter of, chiefly, the cerebral hemispheres but also, in some cases, the brain stem and cerebellum. This cavitation is traversed by many fine threadlike "girders," which prove to be blood vessels enveloped by a layer of glial elements. The encephalic gray matter, both the cortex and basal ganglia, is morphologically intact, although cellular or minor architectural alterations may be found on microscopic examination. The effect of this widespread change is practically a total functional and structural isolation of the basal ganglia from the enveloping cerebral cortex.

The questions as to the essential cause and the pathogenesis of this remarkable state have never been satisfactorily answered. This is probably due to the fact that the clinical history of pregnancy and delivery is often devoid of any significant information. Moreover, by the time death occurs, the lesion is full blown. This situation leaves one uncertain as to the intervening stages through which it passes. The observer is also at a loss to know the early lesion, which, in itself, might suggest its etiology. It is not surprising, therefore, that there is much divergence of opinion as to the predisposing and exciting causes of this condition.

The present writer has had the opportunity recently to study the brains of 3 infants who died only a few hours after delivery, with a somewhat unusual type of hemorrhagic lesion of the encephalic white matter. Certain features of the distribution as well as the nature of these lesions suggest that they may well constitute the early stage of cystic degeneration. For this reason, they are reported with this possibility in mind.

HISTORIC APPROACH TO THE ETIOLOGY OF INFANTILE CYSTIC DEGENERATION

The literature is replete with reports of cases of infants in whom chronic cystic degeneration of the encephalic white matter, not infrequently associated with cortical changes, was found at autopsy. The present survey is not so much concerned with a collection of these reported cases but rather with historic development of ideas concerning the pathogenesis of the lesion itself.

One must begin, of course, with the original report of Virchow,[32,33] who believed that cystic degeneration was a residual of an encephalitic process. This assumption was perhaps not unnatural, since, at the time, there was an epidemic of smallpox. The following year, 2 French investigators, Hayem[13] and Parrott,[24] rejecting this concept of an infectious etiology,

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postulated that the condition was a primary degenerative disorder (athrepsia), possibly developing on a nutritional basis. Jastrowitz[16] began to study certain small yellowish periventricular foci that seemed to be of a similar nature and ultimately came to the conclusion that these foci were not of pathologic significance at all. Meanwhile, as Schwartz[29a] has recently pointed out, he had also noted that, in some of these cases, the infant had been subjected to prolonged labor, thus introducing the concept of dystocia as the possible ultimate cause of cyst formation. But this observation was lost sight of while a series of German histopathologists[3,21,35] drew attention to some characteristic lipoidal changes in the glia, which ultimately came to be interpreted as a normal metabolic process.

Schwartz[26,29] again turned discussion regarding these central changes to the possibility that birth injury might be the cause of chronic infantile cystic degeneration. He pointed out the occurrence of focal hemorrhages in the periventricular white matter and postulated a theory of their causation, which was based upon a presumed difference between intra- and extrauterine pressures. He further elaborated his thesis by concluding that these causative hemorrhages were the result of occlusion (thrombosis) of the internal cerebral veins incident to dystocia with deformation of the skull. This theory has also been supported by Marburg and Casamajor[19] and others.

Possible causes of central cyst formation. The various possible etiologic factors in central cyst formation should be considered briefly before introducing another based on experimental and clinical evidence. (The subcortical cysts associated with nodular cortical atrophy in both early and later life are excluded from discussion in this study. Other investigations by the author[8,10] seem to indicate that such cysts are due to rapid degeneration of the overlying cortical neurons after local ischemia incident to arterial occlusion.) There can be little question but that *hemorrhage* into the centrum is one cause of central cyst formation, as is demonstrated at times after effusions near the lateral ventricles in later life.[11] Insofar as cyst formation after hemorrhage incident to venous channel occlusion is concerned, such cysts are more likely to follow thrombosis of the superior longitudinal sinus rather than occlusion of the internal cerebral veins.[9,10] Norman and Baker[23] have described multiple cyst formation as a residual of equine encephalitis, although the evidence submitted for this conclusion is not fully convincing.

An alternative possible mechanism of central cyst formation is *cerebral anoxia*, as suggested both by experimental and pathologic evidence. The experimental studies of Yant and associates[36] demonstrated that central cysts were delayed residual lesions that appeared after exposure of animals to carbon monoxide gas. Similar findings were noted by Hurst[14] after slow poisoning with potassium cyanide, which is but another form (histiotoxic) of anoxia. Cyst formation in the centrum after cerebral anoxia in adults has also been observed.[1,7]

This idea of an anoxic etiology for cyst formation in early life was also suggested by a case reported by Sternberg.[30] An infant, who subsequently proved at autopsy to have cystic degeneration of the white matter of the brain, had been so severely asphyxiated at birth as to be apparently dead. In the report of Neuburger,[22] an infant born five weeks after its mother had been severely asphyxiated by illuminating gas also proved to have cystic lesions in the cerebral centrum. It is strange that, under these circumstances, Neuburger should hold that this lesion in his own case and in that of Sternberg was of *traumatic* etiology! And this after citing a similar case reported by Maresch,[20] in which softening of the basal ganglia and white matter was found five weeks after the fetus had been asphyxiated in utero when the mother attempted suicide by inhalation of carbon monoxide.

The present writer has given his reasons for belief that some form of anoxia is ultimately responsible for this lesion.[5–7] Benda[2] seems to have come to the same conclusion from his own experience, for he writes: "The asphyxiation of the newborn, resulting in cystic degeneration, can, therefore, be produced by a long-lasting labor, by a cord around the neck, prolapsed cord, breech presentation, or delayed twin birth."

But this is getting ahead of the story. A brief review of 3 cases with acute postnatal hemorrhagic changes in the white matter of

the brain, which are thought by the present writer to be antecedent to cyst formation, is first in order.

REPORT OF CASES

Case 1. A full-term female Negro infant died thirteen and a quarter hours after cesarean delivery, spontaneous respiratory activity having been delayed for an interval of six minutes after birth. It was then grunting and irregular in type until the infant's death. The use of a tracheal catheter with withdrawal of mucus was only partially helpful. The mother was an obese primipara, age 34, who had been a known hypertensive for the previous three years. The pregnancy itself, however, was without known complications; specifically, no vaginal bleeding had occurred. During the seventh month, she had been troubled with blurred vision on 2 occasions, and this was still present at times. Her face, hands, and legs were swollen with edema. A grade III blowing systolic murmur was noted over the left third and fourth intercostal spaces. She had noticed some swelling of the ankles for five days before admission. These signs suggested preeclamptic toxemia. She responded promptly to antihypertensive measures, so that the blood pressure fell to 120 systolic, 80 diastolic; then she became first oliguric and then anuric. At this time, the fetal heart tones were noted to be 90 per minute, regular but weak. The mother's respirations became rapid (52 per minute) and labored and continued so for some eight or nine hours.

The blood chemistry findings during this interval were essentially normal except for a slightly low serum potassium (3.8 mEq. per liter), carbon dioxide (22 mEq. per liter), and albumin (3.4 gm. per cent) and slightly elevated uric acid (7.6 mg. per cent).

A sterile vaginal examination was done, disclosing rupture of the bag of waters with escape of much meconium. The mother was in labor for about three days. For twenty-four hours of this time, labor was marked by persistent abdominal pains. No fetal heart tones could be heard at this time, and the fetus was believed dead. The tones again became perceptible, however, although it was assumed that a state of fetal distress existed. For this reason, a low cesarean section was done under spinal anesthesia three days after admission. The infant survived thirteen and a quarter hours.

An autopsy (No. 55-486) was performed by Dr. Margaret McCarron, resident pathologist, about four hours after death. There were no signs of injury about the head, and the cranium was not deformed. No hemorrhage, extradural, subdural, or subarachnoid, was found. A localized bronchopneumonia was noted in the left lower lobe, presumed to be the result of aspiration. The posterior portion of the foramen ovale of the cardiac septum was still open. Death was considered due to "aspiration pneumonitis."

The exterior of the brain appeared to be definitely congested, with a few scattered patches of extravasated red cells, but otherwise no specific lesions of the brain were found. On coronal section from the tip of the frontal to the occipital pole, there appeared a diffuse hemorrhagic infiltration of the white matter, which involved practically the entire centrum (Fig. 1A), sparing the basal ganglia and internal capsule. The internal cerebral veins were not congested or occluded by a thrombus. While some variation in the intensity of the reaction was noted, it was essentially the same in nature throughout. The white matter of the cerebellum was similarly involved.

Microscopic sections were taken of the cortex and subcortex as well as the cerebral centrum. The blood vessels of the leptomeninges as well as of the brain tissue itself were markedly congested, but this congestion was much more marked in the centrum than in the cortex. The cerebral cortex was edematous with widening of the pericellular and perivascular spaces. Spotty areas of pallor incident to absence of nerve cells were also noted. The white matter of the convolutions as well as the deeper centrum was studded with variously sized but usually small focal hemorrhages (Fig. 1B). These hemorrhages were obviously perivascular and in some instances presented a ring conformation. The larger foci had broken through the perivascular spaces and dissected their way between the radiating nerve fibers. Considerable blood pigment, already engulfed by macrophages, could be seen in the vicinity of these hemorrhages. The relation of the hemorrhagic collection to the blood vessels was well demonstrated by the Perdrau preparations (Fig. 1C and D). The interstitial tissues were also marked by small vacuolar spaces suggesting a mild degree of edema. In the Scarlet red preparation, no free fat was found in the hemorrhagic areas, but, in the deeper portions of the cortex, the collection of cells about the ventricles contained much free fat, apparently enclosed within individual cells.

Comment. In this case, it is clear that the state of the mother during the latter part of her pregnancy had much to do with the lethal lesion of the infant's brain. The rather long history (three years) of arterial hypertension, presence of signs of preeclamptic toxemia, the overresponse to antitensive therapy which precipitated an oliguria-anuria, and the ultimate rapid, labored respirations that ensued on renal failure constituted a chain of clinical events which precipitated signs of fetal distress. The transitory failure of fetal heart sounds and the presence of meconium in the vaginal discharge prior to delivery supported the conclusion that an intrauterine crisis, probably anoxic in nature, had taken place. The infant survived an emergency cesarean section

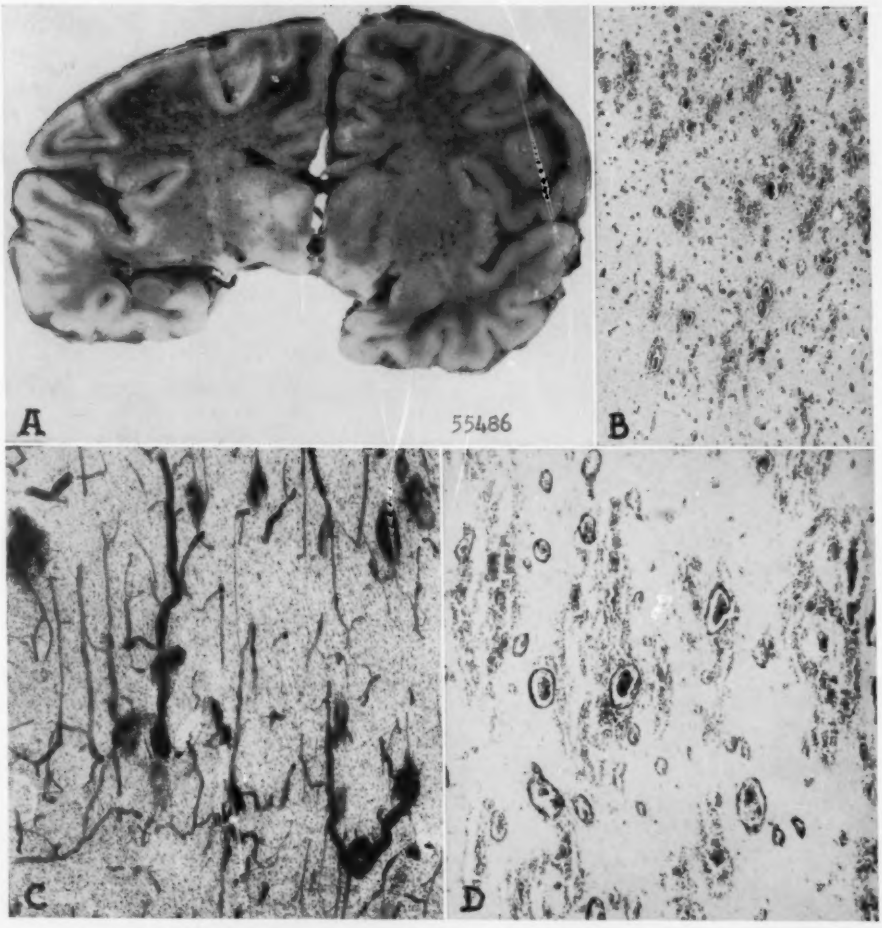

Fig. 1. *Case 1.* (A) Coronal section of cerebral hemispheres showing myriads of petechial hemorrhages. Note sparing of internal and external capsules and less marked changes in temporal lobes. (B) Photomicrograph showing perivascular hemorrhages. PTAH. × 32. (C) Marked congestion of vessels in white matter. Scarlet red stain. × 27.5. (D) Perivascular location of hemorrhages. Perdrau preparation. × 75

for only thirteen and a quarter hours. Many petechial hemorrhages within the cerebral centrum were likewise suggestive of a severe degree of asphyxia, since such lesions are characteristic of asphyxia after exposure to carbon monoxide or nitrous oxide anesthesia.[4] The excessive degree of such hemorrhage as compared with the fatal cases of asphyxia of later life is probably accounted for by the acuteness of the severe anoxial episode and the delicate nature of the central white matter of the fetal brain.

The occurrence of free fat in this case, not in the areas of focal hemorrhage but in the cellular masses about the ventricles, suggests, as others have pointed out, that fatty changes

in the centrum of newborn infants constitute a physiologic and not a pathologic process. The other histologic changes in this instance were identical with those found in the brain of the 2 other infants reported here.

Case 2. A male Negro infant died with signs of marked respiratory distress. During one month of her pregnancy, the mother had chills and fever of unknown cause, possibly malaria. She was nauseated during the entire pregnancy. No fetal movements had occurred for three days before birth. Birth of the child was accompanied by a large amount of meconium escaping from the birth canal. After birth, the child appeared to be hyperactive but the cry was weak. The skin was cyanotic. Several small petechiae were noted in the skin of the left frontotemporal region. As the hours passed, the respirations became progressively slowed and gasping in character. Death came seventeen hours after birth.

The autopsy (No. 57-929) was performed by Dr. J. Settelmayer, resident pathologist. The infant appeared to be normal in its external conformation except for epicanthal folds. It weighed 2.95 kg. The lungs and liver were congested. Septal defects were found between both the auricles and ventricles. In the cranial cavity, a large blood clot was found in the left posterior fossa. The brain, which weighed 350 gm., was submitted to the Cajal Laboratory for further study.

Several focal subarachnoid extravasations were noted over the dorsolateral surface of the cerebral hemispheres, associated with an intense leptomeningeal congestion. The left cerebellar hemisphere was reduced to a shell because of a hemorrhage within its substance. The clot had broken through the cortex and lay in the regional subdural space.

A horizontal section through the cerebral hemispheres disclosed the entire centrum to be stained a brownish color, presumably incident to blood pigment (Fig. 2A). This change appeared to be especially evident in the white matter of the temporal lobes. There was a hemorrhagic cyst in both parietooccipital regions, the walls of which were deeply stained the same color. Other smaller cavitations were noted in the frontal centrum as well, being especially conspicuous at the poles of the lateral ventricles. No evidence of thrombosis of the internal cerebral veins was found.

A study of the microscopic preparations was of unusual interest. As indicated grossly, the blood vessels of the leptomeninges were markedly congested (Fig. 2B). The cortex was edematous, and specific stains showed the nerve cells to have undergone only nonspecific alterations, although a patchy loss of these elements seems to have taken place (Fig. 2 C and D). The hemorrhagic foci in the white matter were primarily perivascular in location, but extension into the surrounding white matter was also common. The number of hemorrhages in a given area also varied from scattered to closely packed extravasations. Some of the larger veins contained collections of fibrin, as though a thrombus was beginning to form. No free fat was noted in the areas of hemorrhage, but some was found in the cellular periventricular zones. Thus, this case seems to correspond closely to the other 2 cases in the nature and degree of structural alterations.

Comment. In this instance, one can only say that the infant experienced fetal distress in utero, as suggested by the presence of meconium in the birth canal at the time of delivery. Moreover, the baby presented signs of severe respiratory distress upon delivery, which persisted with increasing intensity until the time of death seventeen hours later. Whether the mother's period of chills and fever, which lasted for a month during pregnancy, had any bearing on the problem is uncertain. The presence of interatrial and interventricular septal defects may well have contributed to the postnatal anoxic state through a seriously impaired circulation, but some other intrauterine situation was likely to be primarily at fault in this case.

Case 3. A newborn Caucasian male infant was admitted to the Pediatrics Service of the Los Angeles County Hospital one and one-half hours after delivery, the infant having been born in another hospital in this community. The pregnancy had been normal, as had the delivery. The mother had been given a tablet of Demerol every two hours for a period of twelve hours before delivery. Almost immediately after delivery, the infant presented signs of extreme asphyxia that was thought to be due to a mixture of meconium and mucus in the trachea. Respiration was entirely suspended at first, and the use of a respirator failed to restore it. Spontaneous respiration was finally instituted by mouth-to-mouth breathing, but respiratory excursions occurred only at intervals of forty seconds. The infant was then transferred to this hospital. On arrival, he was markedly cyanosed and respirations were grunting in character. Bright red blood was found exuding from the mouth. Examination disclosed rales heard throughout the pulmonary area. A Moro reflex was elicited. In spite of emergency therapy with continued inhalation of moist air and oxygen and use of antibiotics, the infant died forty-one and one-half hours after delivery.

The autopsy (No. 55-798) performed by Dr. Charlotte Tyler, resident pathologist, disclosed a purulent bronchopneumonia, a small, firm vegetation of unknown origin on the tricuspid valve, and generalized congestion of the thoracic and abdominal viscera. The brain was preserved in formaldehyde and subsequently sectioned in the Cajal Laboratory.

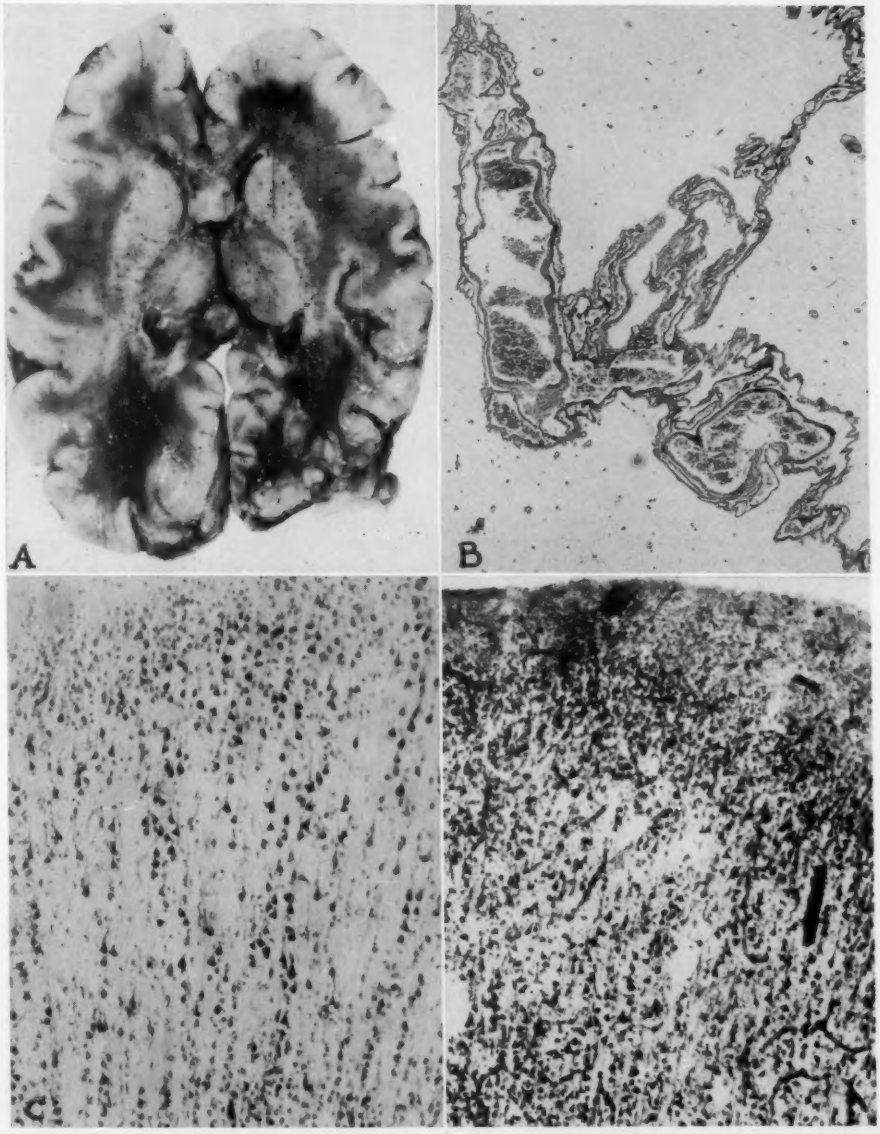

Fig. 2. *Case 2.* (A) Horizontal section of cerebral hemispheres showing petechial hemorrhages anteriorly and gross hemorrhages posteriorly. (B) Marked congestion of meningeal vessels. Perdrau preparation. × 75. (C and D) Showing patchy loss of cortical nerve cells. Nissl and Reduced Silver preparations, respectively. × 125

The leptomeninges were extremely congested. There was no thrombosis of the dural sinuses or their afferent veins. No other external lesions were noted. Horizontal sections through the cerebral hemispheres showed the white matter to have undergone marked but variable degrees of red softening, marked by myriads of petechial hemorrhages (Fig. 3A). Only a very narrow zone of subcortical white matter and a wider and more irregular border about the basal ganglia were spared from this process. Gross cavities filled with clots were found in the parietooccipital region of both cerebral hemispheres. The internal cerebral veins, however, were not thrombosed. The cerebral cortex had entirely escaped, as had the basal ganglia and the brain stem. The cerebellar cortex and centrum of 1 hemisphere, however, were involved in this hemorrhagic process.

Routinely stained sections from the cerebral cortex showed a rather marked degree of congestion of the leptomeningeal vessels and, to a lesser extent, of the vessels of the cortex. The perivascular and pericellular spaces of the cerebral cortex were widened. The cortical nerve cells showed a degree of pyknosis with a tortuosity of their apical dendrites. Sections stained with hematoxylin and eosin and phosphotungstic acid–hematoxylin disclosed an abundance of hemorrhages in the white matter, many of which demonstrated a typical ring conformation (Fig. 3B). In other areas, larger hemorrhages tended to become confluent (Fig. 3C). The latter preparation also showed an occasional collection of fibrin intermingled with red cells, suggesting early thrombus formation in some of the larger veins, although this was by no means the rule. In this case, an early breakdown of tissue was also noted, with the presence of small focal collections of free fat already engulfed by phagocytes (Fig. 3D). Again, fat was more abundant in deep areas of cellular condensations about the ventricles, the lipid material here evidently being of different origin.

Comment. If the history in this case can be taken at face value, the pregnancy and delivery were uneventful. Almost at once, however, a mechanical asphyxia from a mucus plug had developed to a point of respiratory standstill. The attending physician had assumed that this was the result of obstruction by mucus, a conclusion that seems to be borne out by the presence of atalectasis and bronchopneumonia and evidence of hyaline membrane found microscopically at autopsy. Although respirations had been restored after an unknown interval of time, they continued to be grunting and labored, with retraction of the intercostal spaces, and a marked degree of cyanosis persisted. The disclosure at autopsy of an extreme degree of meningeal congestion and the presence of petechial and gross hemorrhages into the cerebral and cerebellar centrums were in keeping with the occurrence of severe anoxia, as were the congestion and a hemorrhagic bronchopneumonia. In this case, there seems to be no acceptable cause for the diffuse cerebral lesion other than a severe degree of asphyxia incident to mechanical obstruction of the alveoli (hyaline membrane) as well as the larger air passages (mucus plug). However, the possibility of some antenatal disorder cannot be entirely excluded.

In both gross and microscopic detail, the structural and cellular alterations in this instance seem to demonstrate its similarity to the other 2 cases reported. This fact seems to indicate that this lesion complex is one that occupies a distinct, though evidently uncommon, place in the alterations in the brain which are to be found after delivery. The uniform history of antenatal (intrauterine) fetal distress and/or a clear history of asphyxia with characteristic symptoms during the survival period (short in these 3 instances) suggest its basis in some form of cerebral anoxia. Its possible relation to the more chronic type of disorder known as chronic infantile cystic degeneration must still be elucidated.

RELATION OF ACUTE CENTRAL HEMORRHAGIC ENCEPHALOPATHY TO PARANATAL ANOXEMIA

In this short series of 3 infants who died shortly after birth, the single uniform lesion found is a widespread, subtotal hemorrhagic necrosis of the cerebral and cerebellar centrums. The remarkable similarity of this change in the 3 cases strongly suggests that we are dealing with a particular and specific type of alteration. That this lesion was the result of some situation having to do with the birth process is further suggested by the fact that the infants presented signs of profound circulatory and respiratory dysfunction throughout their short survival period. The question remains as to what the precise cause of this lesion might be.

In reviewing the clinical data in these 3 cases, certain features are outstanding. In Case 1, a mother with known arterial hypertension gave a history of edema of the soft tissues and ultimately of blurred vision, which suggested a preeclamptic toxemia. As a re-

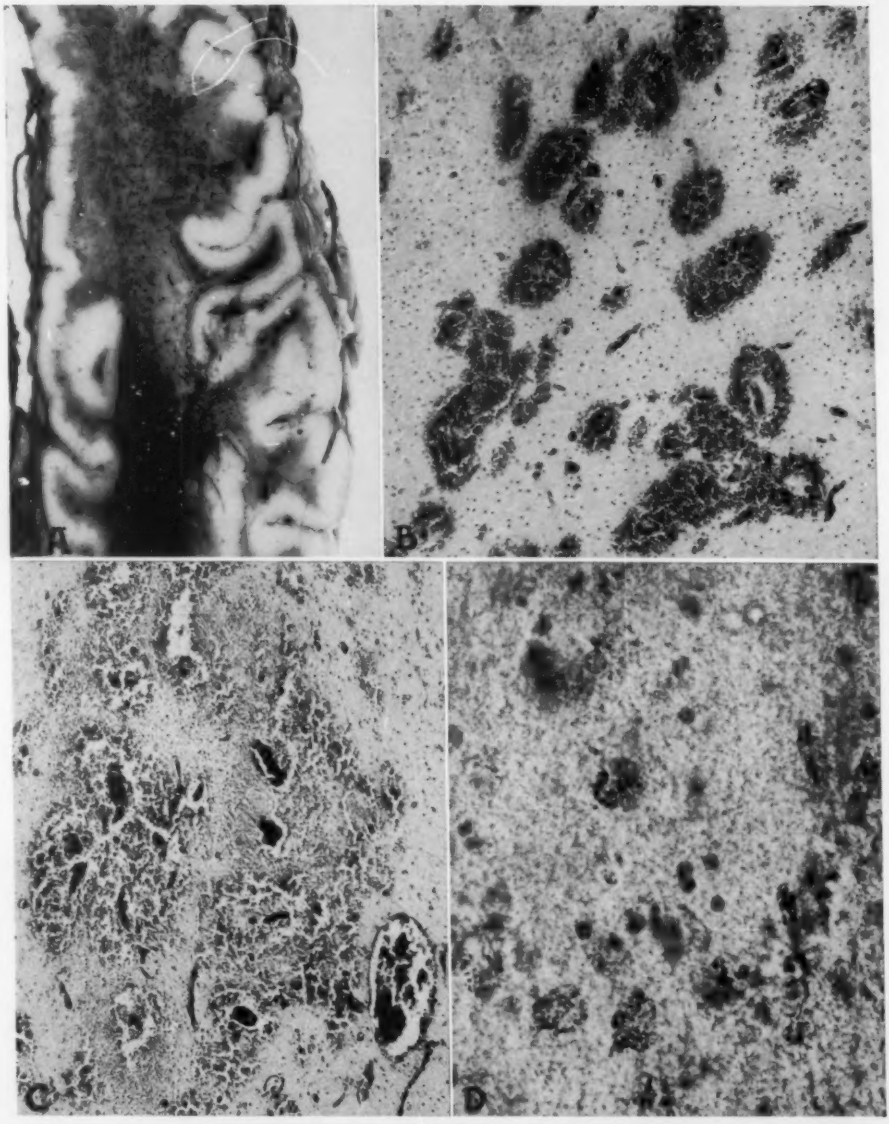

Fig. 3. *Case 3.* (A) Close-up view of horizontal section through the right cerebral hemisphere, showing both petechial (above) and gross (below) hemorrhages. Note hemorrhagic changes well out to cortical margin. (B) Ball and ring hemorrhages in perivascular location. Hematoxylin and eosin. × 75. (C) Confluence hemorrhages. Note focal collections of fibrin (dark areas) within the vessels. PTAH. × 75. (D) Early collection of fat droplets in compound granular corpuscles. Scarlet red stain. × 500

sult of oliguria accompanying a fall in blood pressure, there were signs of fetal distress in utero, which was probably based on a circulatory disturbance and secondary anoxemia insofar as the fetus was concerned. In the second case, the only suggestive birth effect was the evidence that fetal distress had actually been present in utero, although there was no known cause for it. The intrauterine aspect of the problem was further emphasized by the fact that the signs of severe circulorespiratory dysfunction came after a perfectly normal delivery. A downhill course was followed by death after seventeen hours, with the same type of lesion being found in the brain. In the third case, there was an unequivocal asphyxia after birth, incident to mechanical obstruction of the air passages, so that the etiology was clear. After a short survival of forty-one and one-half hours, an identical lesion was found in the brain.

It seems safe to say that the single unifying factor, as far as causation is concerned, is that which concerns the circulation and/or respiration of the fetus or newborn infant. And because it is evident, one may, from experience, anticipate that a failure of either circulation or the respiratory apparatus will result in similar changes in the brain. The fact that petechial or even gross hemorrhages into the centrum are common, even characteristic, lesions in the brain as a consequence of asphyxia, this logic does not seem to be misdirected. The remaining step is to connect this acute and severe widespread hemorrhagic lesion of the cerebral centrum with chronic cystic degeneration of infancy.

CHRONIC INFANTILE CYSTIC DEGENERATION AS A POSSIBLE CONSEQUENCE OF ASPHYXIA

In a previous section of this study, it was pointed out that cyst formation of the cerebral centrum could result from either hemorrhages into this region or the sequelae of asphyxia. There remains yet to note what has actually been found as possible antecedent causes in proved cases of chronic infantile cystic degeneration. It must be said at the outset that, in a number of reported instances of this condition, no definite etiologic factor can be picked out from the information furnished. On the other hand, the actual history of asphyxia at birth is significant. For example, in the case of Jakob,[15] the victim of this condition had been born after version from a transverse position and was asphyxiated in the process. In the case reported by Winkelman and Moore,[34] an infant of 12 weeks was born in an asphyxiated state after prolonged labor. Among the 7 cases from their own files reviewed by Stevenson and McGowan,[31] the first in the series was born with cyanosis and signs of "slight asphyxia." In a case that has been studied by the present writer (Autopsy No. 28-924), this condition was found at autopsy in a 3-year-old child who had been delivered by forceps, with resulting asphyxia.

It must be agreed also, as many other reported cases indicate, that a variety of other intrauterine conditions (including syphilis and other diseases affecting the placenta) may produce similar changes through an interference with the fetal circulation.

To this group of cases, in which asphyxia as a well-defined state occurred after delivery, must be added others in which a history of "difficult labor" is said to have occurred (Meier,[20a] Diamond,[12] and Stevenson and McGowan,[31] Case 4). Still other instances in which a subdural hematoma was also found suggest that labor was indeed difficult and possibly associated with a degree of asphyxia (Köppen[18] and Wohlwill,[35] 4 cases).

A final bit of evidence that should merit consideration is that other lesions, which appear to be residuals of asphyxia before or during the birth process, are not infrequently found to be associated with chronic cyst formation in the infant brain. The coincidence of secondary microgyria is noted in the cases reported by Köppen,[17] Probst,[25] Diamond,[12] and Winkelman and Moore.[34]

Thus, in addition to the fact that, in the recent cases of severe diffuse central hemorrhagic softening reported here, there has been a fairly clear history of circulatory and respiratory difficulties before or during the birth process, one finds a history of asphyxia as such, of difficult labor, or of other signs indicative of a difficult labor if not actually of asphyxia in reported cases of chronic cystic degeneration that also affects in a similar widespread way the cerebral centrum. There remains only the necessity of comparing the 2

lesions in a final move to associate them as the early and late stages of the same process.

ACUTE WIDESPREAD HEMORRHAGIC NECROSIS OF INFANCY AND CHRONIC CYSTIC DEGENERATION OF INFANCY COMPARED

It will be worthwhile to compare various aspects of the 2 lesions here considered. It must be assumed, of course, that 1 is an acute hemorrhagic disorder that may well predispose to a necrosis of the cerebral centrum. Moreover, the fact that the lesion was fatal in these 3 instances would further suggest that, in case of survival from a lesion of this type, the degree of insult to the centrum must be considerably less severe. Finally, it must be recognized that the nature of the lesion and its variation from similar lesions of adult life is dependent upon the immature character of the tissues in question. The striking similarity of the 2 lesions, however, lies in their distribution within the cerebral centrum. When the centrum is rather generally involved, it will be noticed that this process reaches out to and perhaps even includes the subcortical U-fibers. This is also true of advanced cases of chronic cystic degeneration of the cerebral white matter. On the other hand, if any unaltered portion of the centrum is to be found with either of the 2 lesions, it is to be found first in the internal capsule, next adjacent to the basal ganglia anteriorly, then posteriorly, and finally in the external capsule. This zone of unaltered white matter tends to exclude thrombosis of the internal cerebral veins, with consequent red softening incident thereto as a cause of chronic cystic degeneration. With such a cause, the primary region of hemorrhagic necrosis tends to involve first the basal ganglia, particularly the thalamus, and then the adjacent white matter. Occasionally, the white matter extending into the anterior part of the temporal lobe also escapes the process. This wide dissemination of the hemorrhagic process without respect for the distribution of either the external or internal system of arteries or veins would also tend to favor the origin of the process in some circulatory state rather than any blood vessel system. Moreover, the circulatory state most likely to produce such a lesion is an acute asphyxia. This conclusion seems to coincide with the most conspicuous clinical factor in the 3 acute cases presented here and is in accord with what is known about the possible cause of chronic cystic degeneration of the cerebral centrum of infancy.

SUMMARY AND CONCLUSIONS

This study is based upon 3 cases of acute generalized hemorrhagic necrosis of the cerebral centrum of early infancy. The lesions were so severe as to be incompatible with life for more than a few hours. From clinical information present in each instance, it seems logical to conclude that acute anoxemia was the primary cause. This conclusion seems reasonable because, in many instances of acute severe cerebral anoxia, numerous petechial hemorrhages are found in the white matter of the brain. The remarkable similarity of the distribution of the acute lesions in these 3 instances to that of the structural changes found in the so-called chronic cystic degeneration of the cerebral centrum found in infants raises a question of the possible relation of cause and effect of the two. This possible connection is considered in some detail and the question of anoxemia or some gross impairment of the fetal circulation associated with the birth process is reviewed. The most likely answer to this question seems to lie in this possibility.

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Suprasellar epidermoid tumor

A case report with the presenting complaint of see-saw nystagmus

Vernon H. Mark, M.D., J. Lawton Smith, M.D., and Raymond D. Kjellberg, M.D.

INTRACRANIAL epidermoid cysts occur infrequently. They are of pragmatic interest, however, because of the possibility of effecting a clinical cure by their radical removal. Even those tumors with capsules intimately attached to large arteries or brain stem can often be subtotally removed with prolonged relief of symptoms.

Lepoire and Pertuiset[1] have recently presented 100 cases of epidermoid cyst and have carefully reviewed the literature on this subject. They divided their clinical material on an anatomic basis and subdivided the medial suprasellar epidermoids into the pure chiasmal variety and the infundibular group. The former category was described by Olivecrona.[2] These cases present a picture of a slowly progressive primary optic atrophy and bitemporal hemianopsia. This group also may have a normal sella and a dilation of one or both optic canals. Lepoire and Pertuiset[1] describe the characteristic train of endocrine and diencephalic symptoms presented by the infundibular group. Nowhere, however, has anyone described a medial suprasellar epidermoid cyst presenting with see-saw nystagmus. The extreme novelty of this complaint and its dramatic cure by surgical treatment prompted this case report. This is the second case of see-saw nystagmus with histologic verification and the sixth reported case in the literature.

CASE REPORT

M.W., M.G.H. No. 1032980, a 10-year-old white girl, was first admitted to the Massachusetts General Hospital on November 10, 1958. The chief complaint was "twitching eyes" of five months' duration. The girl had been in excellent health until June 1958, when one day a friend happened to notice that the patient's eyes were "twitching." Three months later, school authorities advised an eye examination, and the patient was later referred to this hospital. No other complaints were found except for some difficulty in reading. Recently, she had noted some vertical movement of the print when she attempted to read her school books. The history appeared reliable, and she stoutly denied symptoms for more than four months. Occasional horizontal diplopia had been noted just before admission but was infrequent. She had had no headaches. She denied polydipsia, polyuria, loss of vision, vertigo, sensory or motor symptoms, ataxia, or any other neurologic complaints.

Aside from obesity, general physical and neurologic examinations were within normal limits. On ophthalmologic examination, the corrected visual acuity was 20/200 in the right eye and 20/30 in the left eye. Visual field examination revealed a dense bitemporal hemianopsia. The most striking finding was the abnormal ocular motility. A constant nystagmus with a definite rotatory component was apparent. Although a clockwise rapid phase could be detected, the nystagmus was nearly pendular, rather slow, rhythmic, and about 15° in amplitude. It was present in the primary position and on gaze to both sides but was perhaps more prominent on dextroversion. Very little nystagmus was evident on upward gaze, but a greater amplitude was present on downward gaze. The versions were full, and accommodation and convergence were normal. The right pupil was 4.5 mm. and the left, 3.5 mm.; both reacted normally to light. Spasticity of conjugate gaze[3,4] was noted to the left on attempted lid closure. There was no skew deviation. Opticokinetic nystagmus was intact and equal in all directions. Ophthalmoscopy revealed bilateral primary optic atrophy, more marked on the right.

Repeated testing with cold caloric stimulation, with up to 25 cc. of ice water in each ear, and also with Barany chair rotation produced absolutely no change in the nystagmus. Yet it was consistently suppressed by opticokinetic testing. Otologic consultation revealed no other abnormalities. Laboratory data, including an endocrine study, were unremarkable. Roentgenograms of skull and optic foramina were considered normal. On No-

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This study was supported in part by special traineeship BT-357 from the National Institute of Neurological Diseases and Blindness.

Fig. 1. The mass lesion is clearly outlined in this pneumoencephalogram with the striking indentation and obliteration of the anterior inferior portion of the third ventricle.

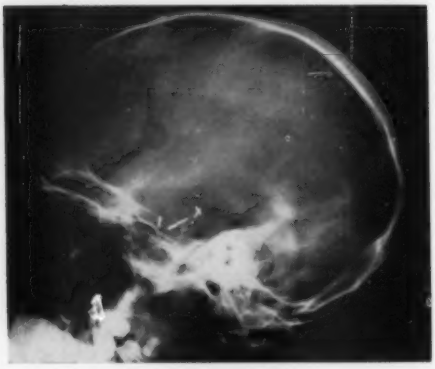

Fig. 2. Clips are attached to the remnants of capsule, and 2 of these are posterior to the posterior clinoid in the region of the prepontine cistern.

vember 20, a pneumoencephalogram revealed a suprasellar filling defect immediately above the diaphragma sella, indenting the anterior inferior portion of the third ventricle (Fig. 1). On November 26, a right frontal craniotomy was performed by 2 of the authors and a suprasellar cyst was encountered; 15 cc. of cheesy material was lifted out of the cyst, and portions of the thin cyst capsule were excised, except for the parts intimately bound to internal carotid artery, hypothalamus, and mesencephalon. When the dissection was completed, only a few capsular remnants remained, one posterior to the posterior clinoid in the prepontine cistern. This and other remnants were marked with silver clips (Fig. 2). Histologic examination of the suprasellar tissue revealed "epidermoid cyst with rupture and foreign body reaction." An uneventful postoperative course ensued, and, by the tenth postoperative day, the see-saw nystagmus had completely disappeared. Vision had improved from 20/200 to 20/30 in the right eye, and definite improvement was noted in the bitemporal field defect.

The patient was seen three and one-half months postoperatively, at which time the see-saw nystagmus was still absent and vision was 20/20–4 in both eyes. There appeared to have been some slight progression in field loss, and the disks were quite pale. The patient is being followed closely to determine if the field loss is due to progression of primary optic atrophy or to further involvement from the pearly tumor.

DISCUSSION

The nature of the nystagmus in this patient was somewhat difficult to evaluate until slow-motion movies, that could be studied carefully, were made. After review of Maddox[5] original description of see-saw nystagmus, it became apparent that our case was indeed similar. His original description cannot be improved and is excerpted as follows:

". . . The appearance of the eyes when viewed from a distance exactly resembled a see-saw, one always rising as the other was falling. On closer inspection the rising of the right eye and the falling of the left eye was seen to be accompanied by conjugate parallel torsion to the left; the falling of the right and rising of the left by parallel conjugate torsion to the right. When I held a hatpin horizontally at the level of the lower margins of the cornea the rise and fall of each eye appeared to be at least 1 mm. The oscillations, both vertical and torsional, are strictly undulatory with nothing saccade about them. Counting 1 wheel movement and its return as a period of oscillation, there were 152 such periods per minute on looking straight forward. On looking up, however, the movements became quicker and smaller and were counted as 204/minute. The vision of each eye is 6/24 and is least confused on looking up, showing that the great amplitude of the excursions is more embarrassing than their greater rapidity. Objects appear to him to move slightly. Diplopia only occasional. Now and then attacks of slight head-nodding are noticeable in the sagittal plane. He has bitemporal hemianopsia with partial inversion of the colour fields. There is some reason to believe that this form of hemianopsia

has lasted in his case for some years. The horizontal balance of the eyes exhibits only slight exophoria, and there is only slight right hyperphoria of a degree sufficiently small to be immaterial. There is, however, excyclophoria of 10 degrees.

"It is noteworthy . . . that the rising and falling of each eye is exactly the opposite of what an anatomical consideration of the muscles would indicate, since extorsion of each eye is accompanied by a fall of the cornea, though the (extorting) superior oblique is a depressor. The see-saw or apparent vertical motion of the eyes in opposite sense is partly an optical illusion due to the greater stretch of visible sclera on the outer side of the cornea than on the inner, but that is not wholly so; it is made evident by the experiment with the hatpin, by the rise and fall of the eyelids, and by a prism device I have made which allows one eye to be seen over the other, and the separation between them vertically to wax and wane alternately."

An additional unreported case of see-saw nystagmus was seen through the courtesy of Dr. Frank B. Walsh.[6] This patient, interestingly, also had a bitemporal hemianopsia. Jenson[7] recently reported 2 cases of see-saw nystagmus, but visual field examination was unsatisfactory in both because the first patient was unable to fix and cooperation was poor in the second. Larsen,[8] in 1957, reported the first autopsied case of see-saw nystagmus. His patient was a 3-year-old boy who, in addition to the nystagmus, presented papilledema on the right and optic atrophy on the left, with right sided spasticity, intention tremor, an abnormal electroencephalogram, and hydrocephalus. Section revealed a large "oligodendrocytoma chiasmatis." In Rucker's[9] case of see-saw nystagmus, the fields are difficult to evaluate, since bilateral chorioretinitis attributed to toxoplasmosis had reduced the visual acuity to less than 3/200 in both eyes. It is thus seen that, in 3 of the 7 known cases of see-saw nystagmus, a definite bitemporal field defect was present; in the fourth case, a tumor was involving the chiasm in a patient too young for accurate visual field examination. Furthermore, each of the 3 other cases (Jenson and Rucker) presented difficulties in visual field evaluation. That the phenomenon is not related to visual acuity per se is seen by the fact that our patient had 20/20 vision in 1 eye and that Maddox' patient had 6/24 vision in both eyes at the time the nystagmus was first observed. Apparently, because of the associated bitemporal hemianopsia, the lesion producing see-saw nystagmus must be somewhere near the region of the third ventricle because of associated bitemporal hemianopsia.

The surgical therapy of intracranial epidermoid cyst is directed toward removing as much of the capsule as possible without putting traction on major blood vessels or vital brain stem structures, which might produce an operative catastrophy. It has been stressed that all the cheesy material must be removed at the time of surgery, since a severe chemical arachnoiditis may result postoperatively when this is not done. Epidermoids are benign tumors, but, if the capsule is not completely removed, they may recur slowly over a period of years. Fortunately, reoperation is usually technically feasible and therapeutically effective.

ADDENDUM

An additional patient with see-saw nystagmus was seen by one of us (V.H.M.) after this manuscript was submitted. A 10-year-old boy with dense bitemporal hemianopsia, see-saw nystagmus, greatly increased intracranial pressure, and a large sella succumbed after frontal craniotomy. At autopsy, a glioma invading hypothalamus and thalamus and protruding into the third ventricle had largely replaced optic chiasm and extended into the sella.

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X-ray radiation of experimental lesions of the spinal cord

C. C. Turbes, D.V.M., L. W. Freeman, M.D.,
and D. C. Gastineau, M.D.

EVEN ON casual observation, it is apparent that trauma to the spinal cord is followed frequently by a severe scarring reaction. Many experimental methods have been used in efforts to alter or avoid this scarring reaction. In these laboratories, grafting procedures have not altered the course of scarring. On the other hand, certain chemical agents, such as pyrogenic substances and the enzyme trypsin, have been noted to alter the patterns of scarring.[1] In the case of trypsin, these effects have been noted when the material was administered intrathecally, intravenously, or intramuscularly.[2] In attempting to evaluate these apparently beneficial influences induced by a variety of agents, it was hypothesized that the reactions must be of a nonspecific nature, since they appeared to act through the same common system. It was felt that a trial with a physical agent whose action on connective tissue was reasonably well explored (such as x-ray on keloid[3]) should be utilized.

The present study reports on the effects of x-ray radiation on certain components of the experimental lesions of the spinal cords of dogs. Special attention has been directed to collagenous, neural, and vascular elements of the scar tissue.

MATERIALS AND METHODS

Healthy adult female dogs of approximately 25 lb. in weight were subjected to laminectomy of the eighth and ninth spinal thoracic vertebrae under strictly aseptic conditions. All of the operations were done by the same operator in order to attain a measure of standardization in the procedure. The dura was exposed, sharply incised in the midline, and held with retraction sutures. The spinal cord was then bluntly transected with a sharp scissors. Hemorrhage was generally controlled by the temporary application of hemostatic material. The dura mater, the lumbodorsal fascia, subcutaneous tissues, and skin were closed separately with interrupted black silk sutures. In 4 animals, the procedure was carried down to the dural incision but no further; 61 animals were carried through the complete transection as is described.

Of the animals, 6 were brought directly from the operating room to the radiation therapy unit while still under anesthesia. They were suspended in a sling stabilized with sand bags. Lead plates were used to shield the body, leaving an aperture 40 mm. square directly over the area of the spinal cord transection. The remaining animals were reanesthetized for radiation; 5 animals were subjected to radiation on the first postoperative day, 8 on the second, and 9 on the third. All of these animals were given 1,000 rads at the lesion. Another 6 animals received 1,000 rads at the lesion on the day after operation and an additional 1,000 rads one week later; 27 animals were handled in the same fashion but were not radiated. The 4 animals that had laminectomy without transection received 1,000 rads on the first postoperative day and an additional 1,000 rads on the eighth.

The animals were given careful nursing care with periodic bladder expression and whatever special considerations were necessary. Despite frequent efforts to put all paralyzed joints

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through a full range of motion, many of the animals developed rather severe contractures around joints. In addition, decubitus ulcers developed on some. Genitourinary tract infections were rather common and were usually treated with antibiotic therapy. The animals were observed for reflex action, evidences of voluntary activity, and general health.

Observations were carried out over a period extending up to three and a half years in 1 animal. At the termination of the observation period or death, as the case may be, the vertebral section containing the specimen was resected and fixed in 10% neutral formalin. The formalin was changed periodically, and the specimens were then dissected free. They were imbedded in paraffin, and serial sections were made. Staining procedures used included hematoxylin and eosin, Mallory triple stain for collagens, Weil's myelin sheath stain, and modifications of the Cajal, Bodian, and Bielschowsky nerve fiber stains. Detailed histologic studies were then made of all of the lesions.

RESULTS

The animals in general showed the usual difficulties encountered in this type of preparation. These included the development of ulceration over bony prominences, genitourinary tract infections, and wounds of fighting. They characteristically showed weight loss that was more severe in those with ulcerative lesions. No great distinctions were seen between the nonradiated and radiated animals, although the 8 animals irradiated on the second postoperative day lived longer as a group and appeared to carry through in better general health. This might also be said about the animals radiated on the third postoperative day. One would be inclined to suspect that prolonged general anesthetics administered so closely together might have played a role, accounting for the better survival of the animals having a longer spacing between their anesthetics. However, since the earliest death was at thirty days, this consideration apparently would not hold.

Typical reflex patterns were observed in all animals at some period in the course of the experiment. Several animals showed early activity reminiscent of voluntary activity, and others showed similar activity later in the course of the experiment.

The 27 control dogs were carried up to four months. Of these, 11 died between the forty-fifth and fifty-seventh day; 8 died between the sixty-third and one hundredth day, 2 were sacrificed between the sixty-third and one hundredth day because of fighting wounds, and the remaining 6 were sacrificed between the one hundred sixth and one hundred twentieth day. Of these latter 6, 2 showed ability to stand but no coordination between the fore and hind limbs, whereas the other 4 showed this coordination, which began to appear as early as one and one-half months postoperatively.

Among the 38 radiated animals, the range of survival was similar to that of the nonradiated animals, with the exception that some of them were carried for considerably longer periods of time; 4 of those subjected to 2,000 rads were sacrificed at one year, 1 at one and one-half year, and 1 at three and one-half years.

Evidences of coordinated activity of the hind quarters with the fore limbs were seen in the majority of animals kept over prolonged periods of time. The 4 animals that did not have transection but were radiated walked without deficit the day following laminectomy and continued in this fashion throughout the year and one-half of observation.

The control animals showed dense adhesive scar of the lesion to the dura mater, obliterating the subarachnoid space. In addition, 7 of the cords showed extensive scarring that extended beyond the surgical lesion and appeared to have concomitant softening of the underlying spinal cord. The scar appeared to obliterate all anatomic detail for approximately 1 cm.

In the animals subjected to radiation, connective tissue appeared lessened throughout the entire path of the surgical approach. In addition, depletion of scar in the spinal cord was quite obvious and was most remarkable in those animals receiving the radiation on the second and third postoperative days and in those receiving 2,000 rads. Any less tendency toward subarachnoid block was not apparent as compared to the control animals.

None of this scarring was apparent in the

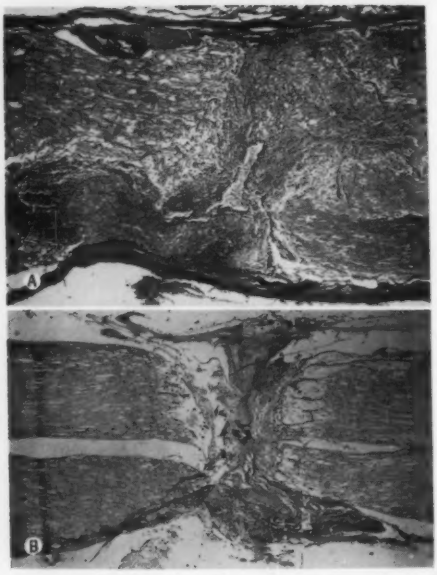

Fig. 1. [A] Control transection (nonradiated) at forty-three days, showing early scar elements and debris. Bielschowsky stain. × 75. [B] Control at sixty-seven days, showing organization of scar into dense barrier. Bielschowsky stain, × 75

animals that were not subjected to spinal cord transection.

In the untreated animals sacrificed within thirty-five to forty-four days, the connective tissue portion of the scar was highly vascular and cellular and contained little collagen. Neuronal debris adjacent to the scar was extensive and mixed with macrophages, capillaries, and reticular-like connective tissue (Fig. 1A). In the animals living up to the sixty-third day, no nerve elements were observed. Neuronal debris adjacent to this scar was largely absent, and there were few axonal retraction balls and phagocytes. Generally, there appeared to be a space between the end of the cord segments and the scar. Occasionally, strands of glial tissue with vessels extended through this space to the scar (Fig. 1B). In cords of animals living beyond sixty-three days, axons were seen extending from the ends of the cord segments along the glial and connective tissue strands and blood vessels through the scar. Many of the neural elements were found within the scar, and some of these were interpreted as undergoing degenerative changes. In 2 of the lesions, nerve fibers were found scattered extensively throughout the scar tissue and seemed to have originated from dorsal and ventral roots. Some of these fibers could be followed into the opposite segment of the spinal cord. Occasionally, nerve fibers were seen to extend into the scar along blood vessels and strands of connective tissue in the region of the anterior median fissure.

In the radiated animals examined early, no particular difference was noted in animals treated on the day of operation and on the first postoperative day when compared to animals in the control group carried a similar length of time. More debris was found in the lesions of the control cords. In the more chronic radiated lesions, vascularity was decreased and the ends of the proximal and dis-

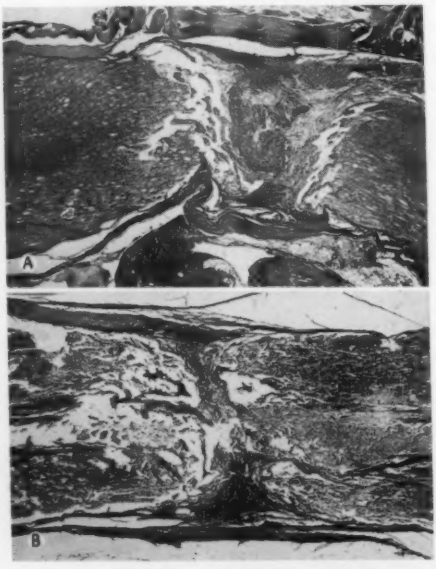

Fig. 2. [A] 1,000 rads on day of operation. Considerable scar in evidence with remnants of neural tissue and neuronal debris (early). Bielschowsky stain. × 75. [B] 1,000 rads on third postoperative day with diminution of scar and considerable numbers of neural elements in area of transection. Bielschowsky stain. × 75

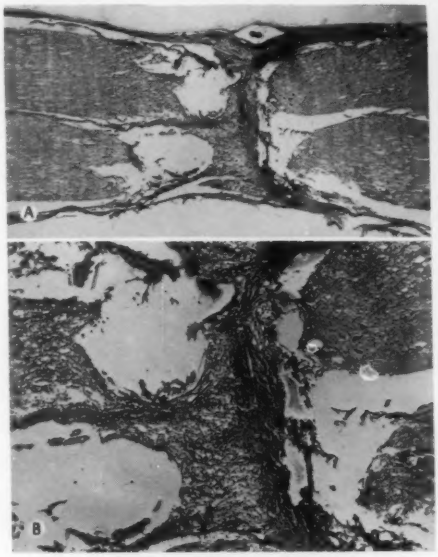

Fig. 3. [A] 1,000 rads on third postoperative day. General diminution of scar and cavitation. Bielschowsky stain, × 75. [B] Neural tissue entering scar from central portion of cord. × 150

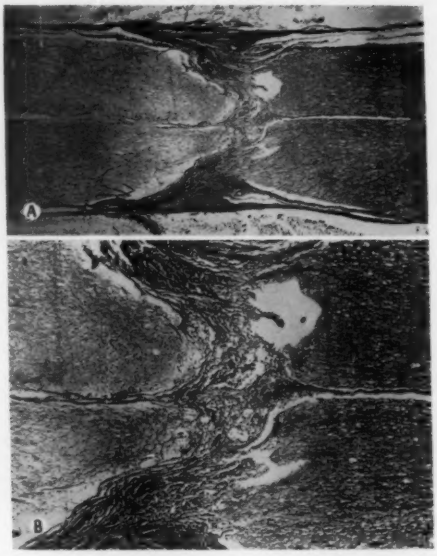

Fig. 4. [A] 1,000 rads on day of transection and 1,000 rads one week later. Central diminution of scar is apparent. Bielschowsky stain, × 75. [B] Neural tissue from central portion of cord in area of transection. × 150

tal segments of the spinal cord were in close approximation to the scar. In these lesions, the glial and connective tissues contained many neural elements. It was impossible to determine whether these elements should not be considered to be degenerating (Fig. 2A). In those animals radiated on the second postoperative day, collagenous connective tissue was quite obviously decreased in density. In 1 of them, a wide space was noted between the scar and the proximal and distal segments of the cord. In 2 of the animals, the space existed between the proximal cord and the scar only. In 5 others, strands of glial and connective tissue containing intact axons were seen between the divided stumps of the spinal cord. Of these axons, 2 could be traced serially back to posterior roots that appeared to have been incorporated in the scar. These fibers entered the distal segment of the spinal cord.

In the 9 animals radiated on the third postoperative day, the scar again appeared less dense and vascular than in the animals radiated on the second postoperative day (Fig. 2B). In 1 lesion, a ventral root appeared to have been cut and carried into the scar. These fibers could be traced into the distal segment of the spinal cord. In another, similar nerve fibers could be traced from the proximal stump into the distal stump and appeared to be of posterior root origin. In this group, 2 animals appeared to have persistent cord tissue that apparently had not been severed at the time of production of the lesion. By comparison to the other animals of this group, there appeared to be less density in the scars of these 2 animals. The remaining 5 animals showed glial and connective tissue containing nerves and blood vessels connecting the ends of the proximal and distal segments of the spinal cord. Density of the scar was quite obviously decreased, especially in the central portion. It tended to be replaced by loose reticular connective tissue.

The 6 animals receiving 2,000 rads showed

generally a greater decrease in collagenous connective tissue (Fig. 3A and B). However, the animal maintained for three and one-half years showed an extensive collagenous scar, but the silk sutures used to close the dura mater were well within the scar and were surrounded by dense connective tissue. In this animal, the scar adjacent to the isolated distal segment of the spinal cord contained a number of neural elements that appeared to be of dorsal root origin. An animal sacrificed at one and one-half years was found to have persistent cord tissue in the left lateral funiculus. The scar in this specimen was not dense centrally, and neural elements crossed the scar area. Numerous blood vessels and connective tissue also crossed this scar area. The 4 animals sacrificed at one year showed decrease in central scarring. Numerous neural elements crossing the scar area were noted, in association with blood vessels and glial and connective tissue (Fig. 4A and B). Some of these elements were quite clearly not of root origin. Several of the animals showed neural elements in the loose scar tissue.

DISCUSSION

This report is intended largely as a measure of the possibility of x-ray radiation influencing the density of the scar at the site of a lesion in the spinal cord. It appears that the answer is in the affirmative. At the dose levels used, no harmful effects were observed.

Greater difficulties were encountered in handling these animals since they were confined to cages, accounting for the rather large number of complications. However, the complications were no greater in the treated than in the untreated animals. No ill effects were noted locally from the radiation, even in the long-term animals, although the hair turned white over the area.

The operator obviously failed to sever some of the more ventrally placed fibers of the cord in a number of animals. Quantitatively, such misses represented no more than 1% of the total cross-section area of the cord. However, it has been observed in the past that such remaining fibers can allow a remarkable amount of walking function.[4,5] Similarly, it has been observed that not a great portion of neural elements need cross a transection to produce a remarkable degree of function.[6] This experiment was definitely not designed with functional results in mind or the surgery would have been far more meticulous in regard to the treatment of the spinal cord during and after transection. However, since the ultimate object in attempting to decrease the density of the scar tissue connecting the divided ends of the spinal cord would be to obtain penetration by growing neural elements, these results tend to indicate that this possibility exists. Such elements may be derived from ventral or dorsal roots, or from so-called internuncial neurons. A criticism that could be offered to the design of the experimentation would center about the large size of the lesion, with the added potential of difference in distances between the divided stumps of the spinal cord. This criticism would probably be most effective were the functional aspects to be foremost in consideration.

Whether these radiation effects are directly upon the cells or operate through some chemical system is not apparent from these studies.[7] Both effects may be in operation. The greater effectiveness of the radiation delivered later would probably indicate that the effects were on the cellular elements of the scar.

Some consideration has been given to the possibility that capillary buds could have been killed by x-ray radiation, contributing to the development of the cystic cavitation. Such inhibition of vascular development has been reported by Merwin and Hill,[8] apparently starting at 1,500 r in superficial wounds. It is possible that destruction of vascular tissue that might serve to bridge the neural hiatus would remove support for growing neural elements. Examination of the sections did not appear to verify this opinion.

Could the radiation levels have impeded axonal growth? Information on peripheral nerves indicates that, at 100,000 r, conduction is not affected, but it is stopped by 200,000 r.[9] Effects would probably be noted at lower levels if the radiation were directed to the nerve cell bodies. The studies of McLaurin, Bailey, Harsh, and Ingraham[10] would indicate that no harmful effects could be expected at the levels of radiation used here.

No specific examination of glial cells was made, but Clemente and Holst[11] showed that

above 4,000 r was required to influence glial cells in the brain.

SUMMARY

In controlled experiments, radiation directed to spinal cord lesions produced surgically showed an effective diminution in the amount and density of the connective tissue scar.

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Postgraduate Course at University of Michigan Medical Center

A postgraduate course in Clinical Neurology will be given April 18 and 19, 1960, at the University Hospital, Ann Arbor, by Dr. Russell N. DeJong and staff of the Neurology Department. Program and application form may be obtained from the Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.

Neurology

BOOK REVIEWS

Surgery in World War II:
Vol. 1. Neurosurgery

Published under the direction of Maj. Gen. S. B. Hayes; editor in chief, Col. John B. Coates, Jr.; editors for neurosurgery, R. Glen Spurling, M.D., and Barnes Woodhall, M.D.; associate editor, Elizabeth M. McFetridge, M.A., 466 pp., Office of the Surgeon General, Department of the Army, Washington, D. C., 1958.

This, the first volume of the history of surgery in World War II, deals specifically with neurosurgery. It has been edited by 2 outstanding neurosurgeons, and many other accomplished men in this field have contributed to the work. This is a documentary volume. The first portion deals with administrative considerations of neurosurgery in the Zone of the Interior, the Mediterranean Theater of Operations, and the European Theater of Operations. The remainder of the book discusses in detail the management of head injuries in these 3 geographic areas. Specific entities considered are: injuries caused by missiles, penetrating wounds of the cerebral ventricles, infections following gunshot wounds of the brain, blast concussion, posttraumatic epilepsy, and speech disorders. There is a chapter on cranioplasty and a final one on clinicopathologic aspects of head injury.

The volume is certainly very well written, but it contains a great deal of statistical and detailed information, some of which is of more interest administratively than clinically. There are many illustrations and tables and 4 appendices.

The authors were selected on the basis of their interest in their special subjects and their previous contributions to them. They have endeavored to record faithfully their mistakes as well as their achievements and have pointed out the major difficulties under which they labored in the war and the possible solutions for them in future wars. They have compiled a treatise which will be an important historical document and which demonstrates the unconquerable spirit that underlay the brilliant record of neurosurgery and head injuries in World War II.

R. N. D.

The Innervation of Muscle

C. Coers and A. L. Woolf, 149 pp., ill., Charles C Thomas, Springfield, Ill., 1959. $9

This monograph will be welcomed enthusiastically by laboratory and clinical investigators of neuromuscular disease. Individual papers published previously had been so scattered through the journals as to make comprehensive coverage of the work difficult. The recent publication is particularly appropriate in view of the lack of attention given the problem at the ARNMD symposium on neuromuscular disorders in December 1958.

The work presents the combined efforts of a Belgian and an English investigator detailing the results of 450 neuromuscular biopsies in

a 149-page volume profusely illustrated with 281 figures. The histology and histopathology of the neuromuscular junction are described and shown. The procedure for human biopsy is given in detail. Vital staining methods are outlined and helpful hints given concerning potential sources of error in procedure and interpretation.

After describing the normal histology and general reactions to disease, the authors present their findings in groups of patients with various neuromuscular diseases—neuropathies, myopathies, and so on. They make invaluable comments on the correlation of histologic examination with results which derive from other disciplines, like the electrophysiology and pharmacology of the neuromuscular junction. Important gaps in knowledge are filled. The concluding chapter on "Application of New Techniques" is thoughtfully done. The publisher is to be congratulated upon the good correlation of illustrations with text, the excellent quality of printing, and the reproduction of photomicrographs.

Only occasionally will the reader need to temper his enthusiasm about the factual detail and its interpretation. However, this may happen during the authors' assessment of the significance of some of their histologic findings. Their teacher (to whom this monograph was dedicated), J. G. Greenfield, and his co-workers of the *Atlas of Muscle Pathology in Neuromuscular Diseases* made a deliberate attempt to avoid using terms such as *degeneration, atrophy,* and *regeneration* which they say, aptly, connote more than they describe.

That there is still a need for such conservatism is witnessed by the disagreement about regenerating muscle fibers in the yet unpublished 1958 ARNMD symposium. A conservative attitude toward interpretation is even more important when the explorations are new. For example, in the present monograph, one might shrink from the statement that changes in myasthenic specimens "have suggested a dysplastic origin." Again, some of the histopathologic correlations could have been drawn upon a more tentative basis, since criteria for diagnosis are sometimes uncertain. Thus, one of the cases of "myositis" appears on later follow-up as a possible Werdnig-Hoffmann disease. In general, one is left with the feeling (drawn from experience with many hopeful procedures of the past) that initial findings of "characteristic picture" and "highly suggestive results" will be tempered as further data accumulate. The authors do point out similarities in the findings between myopathies and neuropathies and between myasthenia and myotonic dystrophy, but one wonders how clear some of the differences reported would be to a histoanatomist unversed in neurologic thinking. Nevertheless, evaluated to this stopping point, the work makes one eager to follow further work done in this area, as, for example, studies of the neuromuscular junction in typical but untreated myasthenia and of the muscle spindle in hypotonic infants.

Despite our reluctance to accept some of the conclusions, as discussed above, this monograph is highly recommended to the readers of *Neurology*. It is to be hoped that, in the near future, American laboratories will attempt to master the laborious procedures and the histologic interpretations so clearly documented here.

L. B.
J. L. O.

Neurological Complications of Lymphomas and Leukemias

by Henry M. Williams, M.D., Lloyd F. Carver, M.D., Henry D. Diamond, M.D., and Herbert Parsons, M.D., 134 pp., ill., Charles C Thomas Co., Springfield, Ill., 1959. $5.75.

This monograph of the American Lecture series presents a careful study of the nature of the neurologic complications of lymphomas and leukemias, the incidence of such complications, and the results of the various types of treatment.

The 4 contributors to the study are or have been associated with the Memorial Center for Cancer and Allied Diseases, New York City. They have reviewed the case material in the records of all patients admitted to the Memorial Center from 1926 to 1956 and, in addition, reviewed all the significant literature. In all, a total of 5,778 cases were reviewed, in which were found 745 patients with 795 neurologic complications. These are classified and treated in separate chapters under the titles of Spinal Cord Compression, Cerebral Manifestations,

Cranial Nerve Involvement, Peripheral Nerve Involvement, Herpes Zoster, Pituitary Involvement, Central Nervous System Infection, and Central Nervous System Hemorrhage. Of special interest is the incidence of torula meningitis in these cases of malignancies.

The chapters are illustrated with tables giving statistical data on the incidence of symptoms under the different type of malignancy and evaluations of the results of current forms of treatment.

Nowhere can all the information available in this book be found in 1 publication; hence, it is invaluable to clinicians and teachers studying and treating this group of diseases. Neurologists who need to be informed on the symptoms and pathology of the different disorders comprising the group of lymphomas and leukemias will find this rewarding reading. There is an extensive bibliography at the end of each chapter for those interested in reading further on special topics.

M.G.M.

Headache: Diagnosis and Treatment

Arnold P. Friedman and H. Houston Merritt, editors, 401 pp., F. A. Davis Company, Philadelphia, 1959. $8

It has been estimated that headache is the chief complaint in more than one-half the patients who seek attention of the physician. Drs. Friedman and Merritt, whose experience in this field is so well known to all neurologists, have edited an important and timely book on this subject.

Drs. Friedman and Merritt have themselves contributed the chapters dealing with "Principles of Pharmacotherapy" and "Migraine." Sections on "Mechanisms of Headache" and "Diagnostic Principles and Methods" are by Dr. E. Charles Kunkle; those on the ophthalmologic, otolaryngologic, and allergic aspects of headache are by Drs. Max Chamlin, D. C. Baker, Jr., and W. B. Sherman, respectively. "Headache in Systemic Disease" is by Dr. John R. Graham; "Headache in Intracranial Disorders," Dr. T. J. C. Von Storch; "Tension Headache," Dr. Charles Aring; "Psychiatric and Psychogenic Factors in Headache," Dr. Lawrence C. Kolb; "The Major Cranial Neuralgias and Surgical Treatment of Headache," Dr. Robert H. Pudenz; and "Role of the Cervical Spine in Headache Pain," Dr. Edward B. Schlesinger.

This is a valuable book for clinicians in all fields of medical practice. As is always true with books of this type, there is a certain amount of discordance in the chapters and some are more complete and helpful than others. Regrettably, there is also a great amount of disparity in terminology and interpretation of certain of the major headache groups. This applies quite specifically to that very common variety of headache known most frequently in this country as either histamine cephalalgia or cluster headache. Dr. Kunkle, for instance, refers to this as a variety of migraine or as intracranial vascular headache, while most of the other contributors refer to it as a specific type of headache, although all feel that no definite relationship to histamine sensitivity has been demonstrated; Dr. Sherman suggests food allergy as a cause of this type of headache. Other similar inconsistencies may be found throughout the book.

Since the vastness of the subject makes it difficult for any one individual to discuss all aspects, this book is a product of a number of physicians in various fields of medicine who have had broad experience in the management of patients with headache. Each author discusses the problem from the viewpoint of his own specialty. An attempt is made to explain the importance or, in many cases, the lack of importance of diseases of various organ systems in the production of headache. Each gives in broad outlines the plan of treatment of patients with headache related to diseases or disorders commonly considered to be in the realm of his specialty. Emphasis has been placed on an explanation of the physiologic and psychologic mechanisms involved in the production of head pain and the importance of correction of disturbances in these mechanisms in the treatment of the patient.

This book is written for the practicing physician. It presents the basic information necessary for the diagnosis and management of the patient with headache. It is a much needed volume and should be of value to every physician who is confronted with headache problems in his practice.

R. N. D.

Sympathectomy — An Anatomical and Physiological Study with Clinical Applications

by P. A. G. Monro, 290 pp., Oxford University Press, London, 1959. $17.25

Most books that cross this reviewer's desk leave him with a pleasant feeling of a well written text, a few occasion perplexity and uneasiness that the reviewer has failed to grasp or understand the thesis, and a rare one arouses an admiration for the clear thinking that brought out a simple and obvious solution of a problem. This monograph falls in the last category.

The study is based upon the patterns of thermoregulatory sweating on 26 cases of thoracolumbar, 12 cases of lumbar, and 12 cases of cervicodorsal sympathectomy as determined by skin resistance. After the appropriate paravertebral sympathectomies, sudomotor activity was found to be present in [a] an "escape" area of the first, second, and, often, third lumbar dermatomes with an occasional extension into a higher dermatome; [b] the perineal distribution of the fourth and fifth sacral dermatomes; and [c] the central area of the face and, at times, the larynx and external auditory meatuses.

The author believes these escape patterns are related to lumbar intermediate sympathetic ganglia that furnish postganglionic cell stations for fibers to the upper 3 lumbar dermatomes. These accessory ganglia have been found at the appropriate levels in a postmortem examination on a previously sympathectomized patient who had persistent sweating.

The perineal sweating is considered due to sudomotor pathways leaving the sacral cord in the fourth sacral anterior root.

The facial sweating is thought to be due to fibers leaving the brain stem via the seventh, ninth, or tenth cranial nerves. The epibranchial placodes associated with these nerves might suggest such a relationship.

The vasomotor effects as measured by plethysmograms were also studied at intervals after sympathectomy. Some activity was retained in the hand in almost 50% of sides examined immediately after operation and was present in all cases in three or more months. In the toes, the vasomotor activity was absent initially after operation but recovered in two to three years in about 30% of cases.

In an appendix, the details of apparatus used for study of sympathetic activity is outlined. A good world list of references is given and an adequate index.

This is a well written and interesting account of the changing state of autonomic functions following sympathectomy. The literature is well presented and critically reviewed. The only criticism of the text as a whole concerns the profusion of case material. Some abbreviation of the histories might have cut the cost of publication of the book and increased its sale. The monograph should certainly be read by all neurologists, neurosurgeons, and internists.

A. E. W.

Intracranial Calcification

by Fermo Mascherpa and Vincenzo Valentino, 150 pp., ill., Charles C Thomas Co., Springfield, Ill., 1959. $9.50

This book, written by two Italian radiologists, is essentially a descriptive account of intracranial calcifications from all usual causes as they are encountered in the ordinary direct roentgenologic examination of the skull. The work is based upon the examination of films from 153 patients in the Milan Neurological Institute and from hospitals in Naples. Included in the material are examples of nonpathologic calcification, calcification in tumors, and pathologic calcifications in the nonneoplastic diseases of the brain and meninges, comprising congenital disorders, parasitic diseases, inflammatory conditions, vascular diseases and anomalies, and endocrine disorders.

Each type of calcification is given brief textual treatment and is illustrated by one or more reproductions of representative roentgenograms. There are well over 100 such illustrations, so the book serves as an atlas as well as an exposition of the subject. For the most part, the reproductions are of reasonably good quality. They have been rendered as positive prints of the x-ray negatives, a reversal of the customary image that some readers may find objectionable. A far more serious defect, however, lies in the text. The authors have written the book in English. Regrettably, their command of English idiom leaves much to be

desired, and the text has obviously received little, if any, editing. As a result, it is slow, difficult reading at best and in places becomes an unintelligible jargon. Because of this unfortunate presentation and the fact that the material itself is already well known to radiologists, neurologists, and neurosurgeons of any experience, the book has little to recommend it.

R. B. R.

Pediatric Neurosurgery

edited by Ira J. Jackson and Raymond K. Thompson, 564 pp., Charles C Thomas, Springfield, Ill., 1959. $16.50

Surgery of the nervous system in children is more than a miniature of adult neurosurgery. In the first place, the lesions encountered differ from those of adult life. Then, the anatomy and physiology of the developing brain are more variable than those of the mature central nervous system. Too, the cardiovascular system and circulating blood present more complex and different problems than their larger counterparts of adult life. In addition to these altered technical problems, the goal of the surgery must be of longer range than that of most adult palliative neurosurgery. In this regard, the surgeon operating upon the immature nervous system has the advantage that the functional recovery from a radical procedure, which in an adult might be crippling, is usually quite satisfactory—in fact, often remarkably good—after a year or two.

For these reasons, the special consideration of pediatric neurosurgery by some 24 specialists is a welcome contribution to the medical literature. The book covers the ancillary fields —anesthesiology, electroencephalography, and plastic surgery—as well as the clinical diagnosis and surgical treatment of neurologic disorders occurring in infancy and childhood.

There is considerable variation in the coverage of their subjects by the different authors. The discussion of brain tumors by Lyle French deserves special comment for its excellence not only in the wide range of material presented but also for its pleasing style. The reviewer had the impression that some authors were discussing adult cases and, in some chapters, found it hard to know just what discussion was based on pre- and what on postadolescent material. On the whole, the subjects were well covered. Perhaps the end results were the least well presented of the various aspects of each disease entity. Most authors followed their cases through the postoperative period, which in surgery of children is only the beginning of rehabilitation.

Lists of references, varying greatly in length, are given after most chapters, but in only 4 chapters are papers published in a language other than English mentioned by the authors. An adequate index is appended.

This is a good account of current American practices in pediatric neurosurgery. It should be in the library of every neurosurgeon. Neurologists, pediatricians, and surgeons will find in its pages much profitable reading.

A. E. W.

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1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

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NEUROPATHOLOGY—April 25, 1960. Dr. Erland R. Nelson. Fees: Juniors: $15.00; Fellows, Actives and Associates: $20.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

CENTRAL NERVOUS SYSTEM INFECTIONS—April 26, 1960. Dr. Charles A. Kane. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

LANGUAGE DISORDERS—April 26, 1960. Dr. Joe Brown. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

GENETICS IN NEUROLOGY—April 26, 1960. Dr. Leonard T. Kurland. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ELECTROENCEPHALOGRAPHY—April 27, 1960. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROLOGIC ASPECTS OF INTERNAL DISEASE—April 27, 1960. Dr. Gilbert H. Glaser. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEURO-OPHTHALMOLOGY—April 27, 1960. Dr. Nathan S. Schlezinger. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

In addition a special review course in Common Neurologic Diseases is offered to General Practitioners on Wednesday, April 27, 1960. The registration fee is ten dollars. Credit will be given by the American Academy of General Practice. **This course is not available to members of the American Academy of Neurology.**

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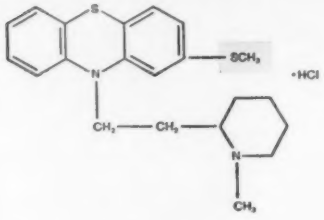

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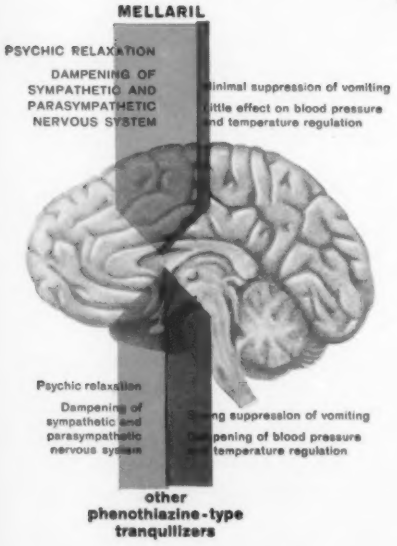

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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

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JANUARY 1960

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Charles M. Poser, M.D., Treasurer

ARNMD Holds Its Thirty-ninth in New York

On Friday and Saturday, December 11 and 12, 1959, the Association for Research in Nervous and Mental Disease held its thirty-ninth annual meeting at the Hotel Roosevelt in New York. The central theme of the scientific sessions was mental retardation. The 1959 ARNMD mission and its many contributors and discussors considered the problem of mental retardation from a multidisciplinary point of view. The principal aspects discussed were developmental processes, genetics, prenatal defects, neonatal injuries, effects of environmental deprivation, and the effectiveness of educational and other forms of treatment methods. The officers for 1959 of the ARNMD were: Lawrence C. Kolb, President; Richard L. Masland, First Vice-President; Robert E. Cook, Second Vice-President; and Rollo J. Masselink, Secretary-Treasurer. A distinguished visitor from abroad, serving on the 1959 Commission, was Jerome Lejeune of Paris who gave a presentation on "Somatic Chromosomes in Mongolism."

Houston Neurological To Hold Eighth Annual Symposium

William S. Fields, Chairman of the Symposium Committee, announces that the Eighth Annual Symposium of the Houston Neurological Society will be held in the Texas Medical Center (March 10-12, 1960). The scientific sessions will be devoted to "Prenatal and Perinatal Factors in Neurological Disease" and to "Pathogenesis and Treatment of Hydrocephalus." Among those who will participate are: S. Hicks (Boston); R. Blattner (Houston); M. Nelson (San Francisco); W. F. Windle (Bethesda); G. Anderson (Providence); D. Matson (Boston); and R. Pudenz (Pasadena).... All interested clinicians and research workers are invited to attend and participate in the discussions. The registration fee is $10.

French International Neurological Reunion To Be Held in Paris

The French Society of Neurology (Société Française de Neurologie) will hold its Twenty-fourth International Neurologic Reunion in Paris (May 31-June 1, 1960). The central theme of the program is "The Apraxies," under the direction of H. Hecaen of Paris. There will also be sessions devoted to the presentation of free papers....All members, French or foreign, of the French Society of Neurology may attend the reunion without

payment of the registration fee. Associate and honorary members of foreign title who wish to attend the reunion are requested to register with the Secretary-General before April 1, 1960, in order that they may receive a printed program and the printed volume of reports on the central theme. Neurologists, French or foreign, who are not members of the Society, may attend the sessions upon registration and the payment of a fee of 2,500 francs ($5.00).... Inquiries and registrations (before April 1, 1960) should be addressed to the Secretary-General of the Society, Docteur J. Sigwald, 68, boulevard de Courcelles, Paris XVII^e^. Payment of fees should be made to the Society Treasurer, M^me^ le Docteur Sorrel-Dejerine, 123, rue de Lille, Paris VII^e^.

Poser Girdles the Globe Peripatetic Charles M. Poser, AAN Treasurer and Executive Medical Officer of the World Federation of Neurology, recently encircled the world in his program of implementing international research in neurology. His itinerary began in Antwerp, included stops in London, Bethesda, and San Francisco; then on to Tokyo, Bangkok, Bombay, Moscow, and finally back to Antwerp. In Tokyo he was able to attend and address the first meeting of the Japanese Association of Clinical Neurology initiated by Professors Okinaka (Tokyo) and Katsuki (Kyushu). Among others in Japan with whom he had the good fortune to chat were Professors Aizawa (Keio), Myake (Kyoto), Katsunuma (ex-president of Nagoya University), and Tamiya (president of the Japanese Association of Medical Sciences). Dr. Poser also had fruitful conversations with Professor Shiraki, recently appointed Professor of Neuropathology at the Institute of Brain Research of the University of Tokyo....In Bangkok, Dr. Poser visited both the Siriraj and Chulalongkorn Medical Schools. At the former he conversed with Professor Chitt Tuchinda; at the latter, with Professor Bunliang Tamthai (who trained in neuroanatomy at the University of Michigan and worked with Russell N. DeJong). He also interviewed Dr. Hatai Chitanondh (Philadelphia trained), who is the head of the neurology section at the Sondet Chaophya Hospital, a governmental institution, and Dr. Prasop Ratanakorn, Director of the Prasat Hospital for Neurological Disorders.... In Bombay, Dr. Poser found a compact, enthusiastic, and well-trained group of neurologists and neurosurgeons and neuroradiologists, many of whom were trained at Queen Square. The senior member of the Bombay group is Dr. Eddie Bharucha, Director of the Neurological Unit of the K. E. M. Hospital. Associated with him are Drs. H. Dastur, neurosurgeon, and Anil Desai, neurologist and electroencephalographer. The smaller neurologic unit at the J. J. Hospital program is directed by N. H. Wadia, who is an authority on tropical neurology. Also on the staff are Drs. Gajendra Sinh, neurosurgeon (trained by Chandy in Velore) and Jimmy Sidhva, neuroradiologist (trained by Bull in London). At the Tata Memorial Hospital, organized by the Indian Medical

Research Council, there are a neuropathologist and a neurochemist--Dr. C. G. S. Iyer (trained by Raymond D. Adams in Boston) and Dr. D. K. Dastur, trained with Seymour S. Kety in Bethesda.... In Moscow, Dr. Poser was received by Professor S. A. Sarkisov, Director of the Moscow Brain Institute, President of the All-Union Federation of Psychiatry and Neurology and a member of the U.S.S.R. Academy of Medical Sciences. With Professor Sarkisov was Dr. Anatoly Raben, Chief of the Editorial Staff of the Department of International Scientific Relations of the Russian Academy. Poser toured the Moscow Brain Institute with Professor Trofimov, the Assistant Director; and the Moscow Institute of Neurosurgery in the company of Professor Ugrumov, one of its Vice-Directors.

Stern Wins Neurosurgical Award Jack Stern of Seattle was the winner of the Fifth Annual American Academy of Neurological Surgery Award for his paper, "Inhibition of the Muscle Spindle Discharge by Ventrolateral Thalamic Stimulation and Its Relation to Parkinsonism"....The Academy now announces its Sixth Annual Award which shall be given for the best paper submitted on a topic of clinical or laboratory research related to the nervous system. The recipient of the award will be invited to present his paper at the Twenty-second Annual Meeting of the Academy in Boston (October 5-7, 1960). The award carries an honorarium of $100, reimbursement of travel expenses (within the continental limits of the United States) to the Boston meeting, and payment of expenses while attending the meeting. The purpose of the award is to attract younger neurosurgeons to research during or immediately after their training. Board-certified neurosurgeons are not eligible....Candidates should submit manuscripts before July 15, 1960, to Dr. Robert McLaurin, Secretary, American Academy of Neurological Surgery, Cincinnati General Hospital, Cincinnati 29, Ohio.

Alajouanine Welcomes Neuropathology Commission in Paris On October 24, 1959, Prof. Th. Alajouanine was host to the WFN Commission of Neuropathology at their first meeting held in the Pinel Library (formerly the consultation chamber of J.-M. Charcot) of the Hospice de la Salpêtrière. After Professor Alajouanine's words of welcome, Dr. Ludo van Bogaert, President of the World Federation of Neurology addressed the members of the Commission,[1] both in French and English, delineating the general aims of the several Problems Commissions of the WFN and of the Commission of Neuropathology in particular. Thereupon, Professor Bertrand of Paris took the Chair. The Commission was formally organized; discussed at some length was the problem of training neuropathologists throughout the world,

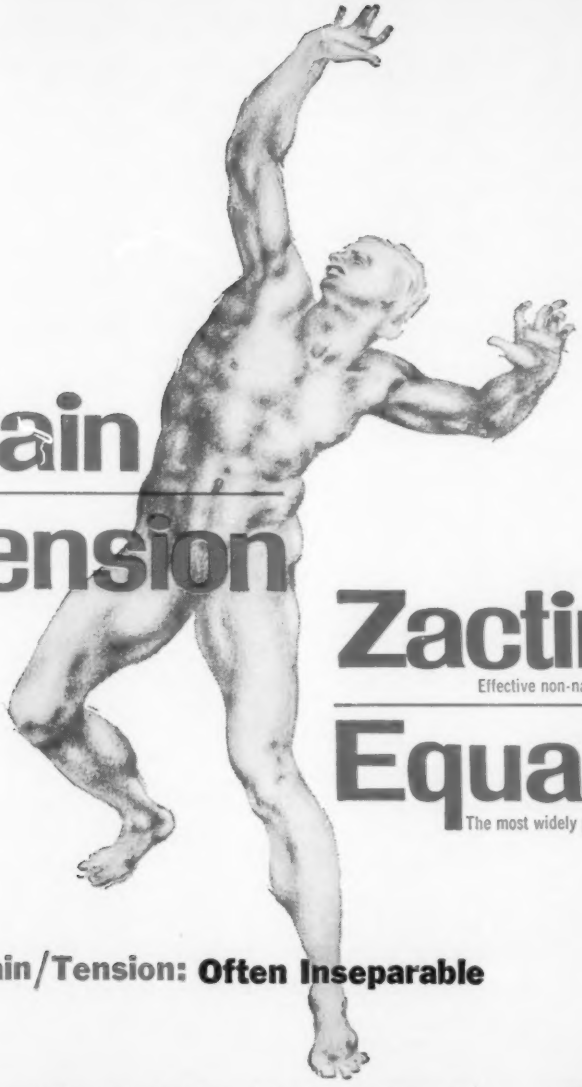
[1]The members of the WFN Neuropathology Commission are: Bertrand (France), Christensen (Denmark), Diezel (Germany), Girard (France), Haymaker (U.S.A.), Løken (Norway), Lüthy (Switzerland), McMenemey (Great Britain), Osetowaska (Poland), Seitelberger (Austria), Sourander (Sweden), Trelles (Peru), Verhaart (Netherlands), and Peters (West Germany).

and some proposals were made for the publication of a European journal of neuropathology, to be published in several languages. This project is being pursued by Professor F. Seitelberger (Vienna), who is secretary of the Commission. On the same day, Professor Alajouanine entertained the group with a luncheon "en champagne" in the Charcot library of the Salpêtrière. That evening, members of the Commission foregathered for dinner at the celebrated French restaurant, "La Pérouse," where they were received by their hosts: Alajouanine, Bertrand, and van Bogaert.

Second National Congress To Be Held in Havana The Cuban Society of Neurology and Psychiatry will hold its Second National Congress in Havana in conjunction with the Second Annual Reunion of the Caribbean Neurosurgical Society (January 13-17, 1960). The scientific program will include symposia on brain tumors, advances in neurology as well as round-table discussions on epilepsy. There will also be an opportunity for the presentation of free papers. One day will be devoted to a consideration of organization and education in neurology and psychiatry, including a discussion of the position of neurology in hospital and medical practice. The current president of the Cuban Society of Neurology and Psychiatry is Ricardo Jimenez Malgrat; the secretary, Jose A. Argain. The postal address is: Colegio Medico Nacional; 23 YM, Vedado; Havana, Cuba.

Address Changes of AAN Members The Executive Offices of the American Academy of Neurology reports that certain Academy members do not advise the AAN Executive Secretary when making a change of address. The new addresses are usually located in a course of time, but currently, in spite of searching, the addresses of two AAN members are unknown: David A. Prince and James B. Webb. It would be appreciated if these members would forward their new addresses to: Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 4307 East 50th Street, Minneapolis 3, Minn.

Reece Bailey



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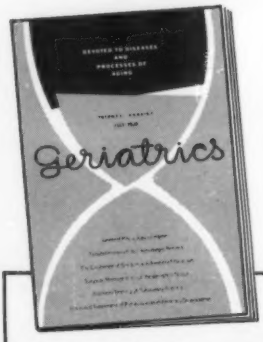

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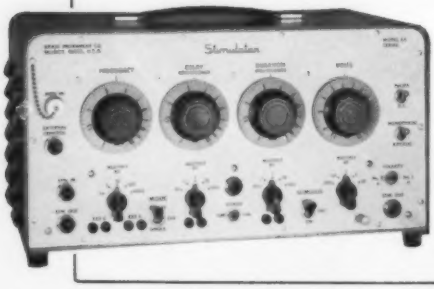

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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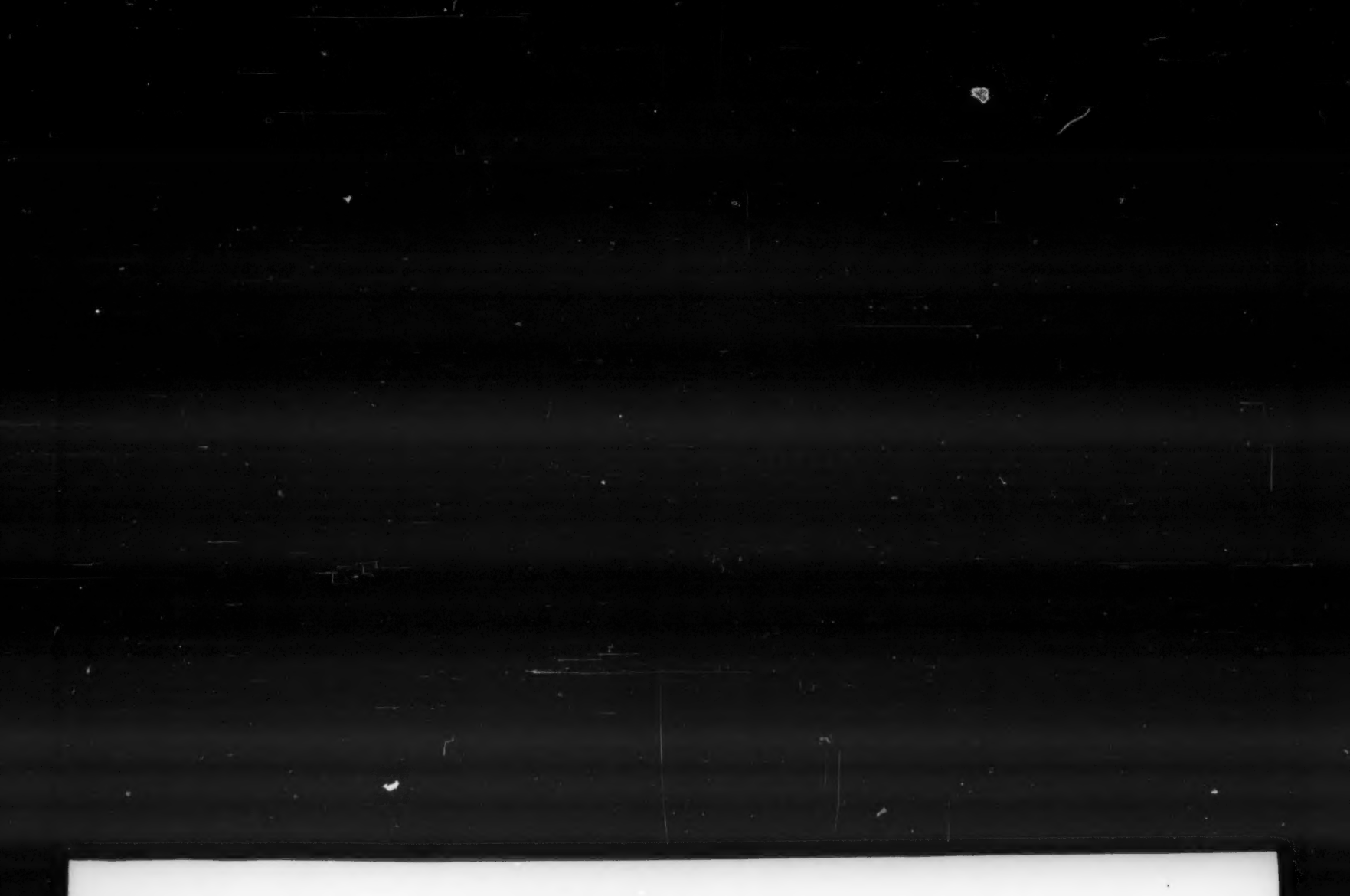
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